ARCHIVES OF

NEUROLOGY AND PSYCHIATRY

DECEMBER 1943

CONTENTS

OTHER PERIODICAL PUBLICATIONS
of the American Medical Association

AMERICAN MEDICAL ASSOCIATION

535 North Dearborn Street   CHICAGO 10

CONTENTS

OTHER PERIODICAL PUBLICATIONS
of the American Medical Association

AMERICAN MEDICAL ASSOCIATION

CONTENTS

CONTENTS

OTHER PERIODICAL PUBLICATIONS
of the American Medical Association

AMERICAN MEDICAL ASSOCIATION
535 North Dearborn Street   CHICAGO 10

CONTENTS

OTHER PERIODICAL PUBLICATIONS
of the American Medical Association

AMERICAN MEDICAL ASSOCIATION

535 North Dearborn Street   CHICAGO 10

CONTENTS

OTHER PERIODICAL PUBLICATIONS
of the American Medical Association

AMERICAN MEDICAL ASSOCIATION

535 North Dearborn Street   CHICAGO 10

CONTENTS

OTHER PERIODICAL PUBLICATIONS
of the American Medical Association

AMERICAN MEDICAL ASSOCIATION

535 North Dearborn Street   CHICAGO 10

CHEMOTHERAPY OF INTRACRANIAL INFECTIONS

II. CLINICAL AND PATHOLOGIC EFFECTS OF INTRACRANIAL INTRODUCTION OF SULFANILAMIDE, SULFATHIAZOLE AND SULFADIAZINE IN NORMAL DOGS

WILLIAM F. MEACHAM, M.D.

RALPH ANGELUCCI, M.D.

EDMUND BENZ, M.D.
AND
COBB PILCHER, M.D.
NASHVILLE, TENN.

In a previous paper,[1] a preliminary report of early experiments was presented because it was felt that a high incidence of convulsions following the implantation of sulfathiazole on the cerebral cortex made immediate publication of that observation advisable.

In this report, additional data on the previously reported experiments and on a number of additional related experiments will be presented. One hundred and fifteen experiments on dogs form the basis of this paper. The study was designed to determine the clinical and pathologic effects of sulfanilamide, sulfathiazole and sulfadiazine on the brain and its coverings.[2]

METHODS AND RESULTS

All operative procedures were carried out with aseptic technic, and any indication of infection was investigated by means of cultures of the cerebrospinal fluid and of material from the wound and the brain obtained during life and at necropsy. Several experiments in which infections developed were not included.

Such clinical factors as pulse rate and body temperature were recorded, but showed no significant alterations. The eyegrounds presented no change in a number of experiments. Weakness, paralysis and reflex changes were observed only in animals which had severe convulsions.

A few animals were allowed to recover, but most of them died or were killed. At necropsy, gross pathologic changes were recorded and blocks of tissue placed in various fixatives. Sections of dura mater and of cerebral tissue were stained

1. Pilcher, C.; Angelucci, R., and Meacham, W. F.: Convulsions Produced by the Intracranial Implantation of Sulfathiazole: Preliminary Report, J. A. M. A. **119**:927 (July 18) 1942.

2. The sulfathiazole was supplied by E. R. Squibb & Sons, New Brunswick, N. J., the sulfadiazine, by Lederle Laboratories, Inc., Pearl River, N. Y., and the microcrystalline sulfathiazole and sulfadiazine, by Smith, Kline & French Laboratories, Philadelphia.

by four to eight technics for demonstration of various cellular and interstitial structures. All microscopic sections were examined independently by two of us, and changes were recorded on a 1 to 4 plus basis. Any differences between observers were reevaluated.

The 115 experiments on dogs fall into twenty groups, which may be further subdivided on the basis of the dose of the drug and the duration of the experiment. The numerous variants make it necessary to present the results in detailed tables and to confine the text to descriptions of the changes which were usually observed.

A. Control Experiments (table 1).—These experiments serve as a basis for distinguishing between the effect of the operative procedure alone, the effect of an inert substance (kaolin) and the effects of the sulfonamide compounds employed in subsequent experiments. No convulsions were produced by the operation (exposure of one cerebral hemisphere) or by the placement of kaolin on the cortex, nor were there other significant clinical results. The operative procedure resulted in fibrosis in the dura, a mild transitory inflammatory reaction in the pia mater and occasionally superficial gliosis in the cortex (fig. 6).

In the experiments with kaolin, a violent inflammation in both the dura and the pia resulted, and in 1 animal the underlying cortex showed fibrosis and changes in the microglia and in the nerve cells.

B. Intravenous or Oral Administration of Sulfonamide Compounds.—Our observations confirmed those of many previous investigators that sulfanilamide and sulfadiazine appear promptly in significant therapeutic concentrations in the cerebrospinal fluid, but that sulfathiazole appears in the cerebrospinal fluid only in barely perceptible quantities (tables 2, 3 [experiments 1-3] and 4).

C. Application of Sulfonamide Compounds to the Intact Cerebral Cortex.—The drugs were placed on the cerebral cortex through a dural incision, which was subsequently closed. The dose varied from 10 to 66 mg. per kilogram of body weight. Experiments were terminated at intervals of a few hours to six months.

The outstanding clinical manifestation was the violent convulsions produced by sulfathiazole. These seizures presented a classic jacksonian "march," usually beginning in the muscles of the opposite side of the face. They were roughly proportional in frequency and severity to the amount of sulfathiazole placed on the cortex.[1] Pronounced salivation invariably occurred during and between the seizures. Such attacks were not produced at all by sulfanilamide and in only 1 animal by sulfadiazine (tables 2, 3 [experiments 1-3] and 4).

All of the drugs were absorbed slowly, as indicated by low concentrations in the blood and cerebrospinal fluid. At necropsy, in the shorter experiments, sulfanilamide and sulfadiazine remained as a soft paste and sulfathiazole as a hard, almost stony, plaque. Sulfanilamide seldom remained grossly visible more than forty-eight hours, but the other two drugs persisted, apparently little changed, for a week or longer.

With sulfanilamide and sulfadiazine the cell count of the spinal fluid was normal or slightly elevated in all but 2 experiments (860 and 7,280 cells per cubic millimeter). Cultures were sterile in both these experiments. With sulfathiazole, however, there was notable pleocytosis in many animals, even with the smallest dose of the drug, the highest count being 2,260 per cubic millimeter.

After the first twenty-four hours, the dura was almost invariably adherent to the cortex (the intermediate mass of drug being included), and the adhesions were more extensive and dense than those in the control experiments. Sulfathiazole was frequently walled off in a sort of fibrous sheath.

TABLE 1.—*Data on Control Experiments*

Type of Experiment	Dog No.	Amount of Drug per Kg. of Body Weight, Mg.	Duration of Life or Observation *	Convulsions	Gross Pathologic Changes			Microscopic Pathologic Changes										
								Dura Mater				Drug Crystals in Pia Mater	Acute or Subacute Leptomeningitis	Cerebral Cortex				
					Drug Remaining	Subcortical Hemorrhage	Corticodural Adhesions	Drug Crystals	Acute or Subacute Inflammation	Interstitial Hemorrhage	Fibroplasia			Subcortical Hemorrhage	Proliferation of Astrocytes	Proliferation of Oligodendrogliocytes	Microglial Changes	Degeneration of Neurons
1. Operation; no drug	DP 7	0	48 hr. K	—	—	—	—	—	—	+	+	—	+	—	—	—	—	—
	DP 8	0	48 hr. K	—	—	—	—	—	+	+	—	—	+	+	—	—	—	—
	DP 21	0	1 wk. K	—	—	·	+++	—	+	—	+	—	+	—	—	—	—	—
	DP 25	0	1 wk. K	—	—	—	++	—	—	—	+++	—	—	—	—	—	—	—
	DP 10	0	2 mo. K	—	—	++	++	—	—	—	+++	—	—	—	++	+	—	—
	DP 9	0	3 mo. K	—	—	—	—	—	—	—	—	—	—	—	+	—	—	—
2. Kaolin on cortex	DP 16	60	48 hr. K	—	+++	—	—	+++	++++	—	—	+++	+++	—	—	—	—	—
	DP 17	60	48 hr. K	—	+++	—	—	+++	++++	—	—	+++	++++	—	—	—	—	—
	DP 18	60	1 wk. K	—	+++	+	++	+++	++++	—	++	+++	++++	+	—	—	—	+
	DP 19	60	1 wk. K	—	+++	—	—	—	+++	++	+	+	+++	+	—	—	+++	++

* In this table, and in the accompanying tables, K indicates the animal was killed; D, that it died, and R, that it recovered.

TABLE 2.—*Data on Experiments with Sulfanilamide*

Type of Experiment	Dog No.	Amount of Drug per Kg. of Body Weight, Mg.	Duration of Life or Observation*	Convulsions	Max. Drug Level in Cerebrospinal Fluid, Mg. per 100 Cc.	Max. Drug Level in Blood, Mg. per 100 Cc.	Max. Cell Count in Cerebrospinal Fluid	Drug Remaining	Subcortical Hemorrhage	Corticodural Adhesions	Drug Crystals (Dura)	Acute or Subacute Inflammation (Dura)	Interstitial Hemorrhage (Dura)	Fibroplasia (Dura)	Drug Crystals in Pia Mater	Acute or Subacute Leptomeningitis	Subcortical Hemorrhage (Cortex)	Proliferation of Astrocytes	Proliferation of Oligodendrogliocytes	Microglial Changes	Degeneration of Neurons
1. Intravenously (sodium salt)	WM 15	50	30 hr. R	—	2.2	3.4	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
	WM 16	50	30 hr. R	—	2.6	3.4	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
2. By gastric tube	WM 11	50	30 hr. R	—	2.3	3.5	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
	WM 12	50	30 hr. R	—	4.0	6.3	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
3. On cortex	WM 7	66	24 hr. K	—	0.5	0.9	4	++++	—	—	—	+	+	—	—	+	—	—	—	—	—
	WM 8	66	24 hr. K	—	0.9	1.3	860	++++	+	—	—	+	+	—	—	++	+	—	—	—	+
	WM 13	66	48 hr. K	—	1.1	1.9	38	++++	—	++	—	+	+	—	—	+++	+	—	+	+	+++
	WM 14	66	48 hr. K	—	1.2	1.6	22	++++	++	++	—	—	—	++	—	+++	++	—	++	++	+++
	WM 1	66	1 wk. K	—	0.4	0.5	3	—	++	++	—	—	—	++	—	+++	++	++	++	++	+++
	WM 2	66	1 wk. K	—	0.6	0.7	3	+	+	++	—	—	—	++	—	+	+	+	++	++	++
	WM 9	10	2 wk. K	—	Trace	Trace	12	—	—	++	—	—	+	—	—	++	+	—	—	—	—
	WM 10	10	2 wk. K	—	Trace	Trace	10	—	—	+	—	+	+	++	—	++	++	+	++	++	+
	WM 6	10	7 wk. D	+	Trace	Trace	..	—	—	—	—	—	—	+	—	—	—	—	—	—	—
	WM 5	10	2 mo. K	—	Trace	Trace	..	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	WM 4	10	4 mo. K	—	Trace	Trace	3	—	—	++	—	—	—	++	—	—	+	+	+	+	+
	WM 3	10	6 mo. K	—	0.4	0.4	7,284	+	—	++	—	—	—	+	—	—	+	+	—	—	+
4. In area of cortical excision	WM 21	10	1 wk. K	—	Trace	0.5	252	—	—	..	—	..	..	..	—	++	+++	..	+++	+++	++
	WM 22	10	1 wk. K	—	Trace	Trace	343	—	—	..	—	..	+	..	—	++	++	+	+++	+++	++
	WM 20	10	2 wk. K	—	Trace	Trace	6	—	—	+++	—	—	+	+++	—	++	++	+	++	++	++
	WM 17	10	2 mo. K	—	0.5	0.5	1	—	—	+++	—	—	+	+	—	++	++	—	++	++	+++
	WM 18	10	2 mo. K	—	Trace	0.5	3	—	—	++	—	—	—	—	—	+	—	—	—	—	+++

* See footnote to table 1.

Microscopically (tables 2, 3 [experiments 1-3] and 4), neither sulfanilamide nor sulfadiazine crystals were seen in the dura or the pia mater. Sulfathiazole crystals, however, were noted in the dura in 9 of 26 animals and in the pia in 4 animals. The crystals appeared as elongated strands, bound together by fibrinous or, later, fibrous bands (fig. 1). They were seen in animals killed as long as one month after implantation of the drug.
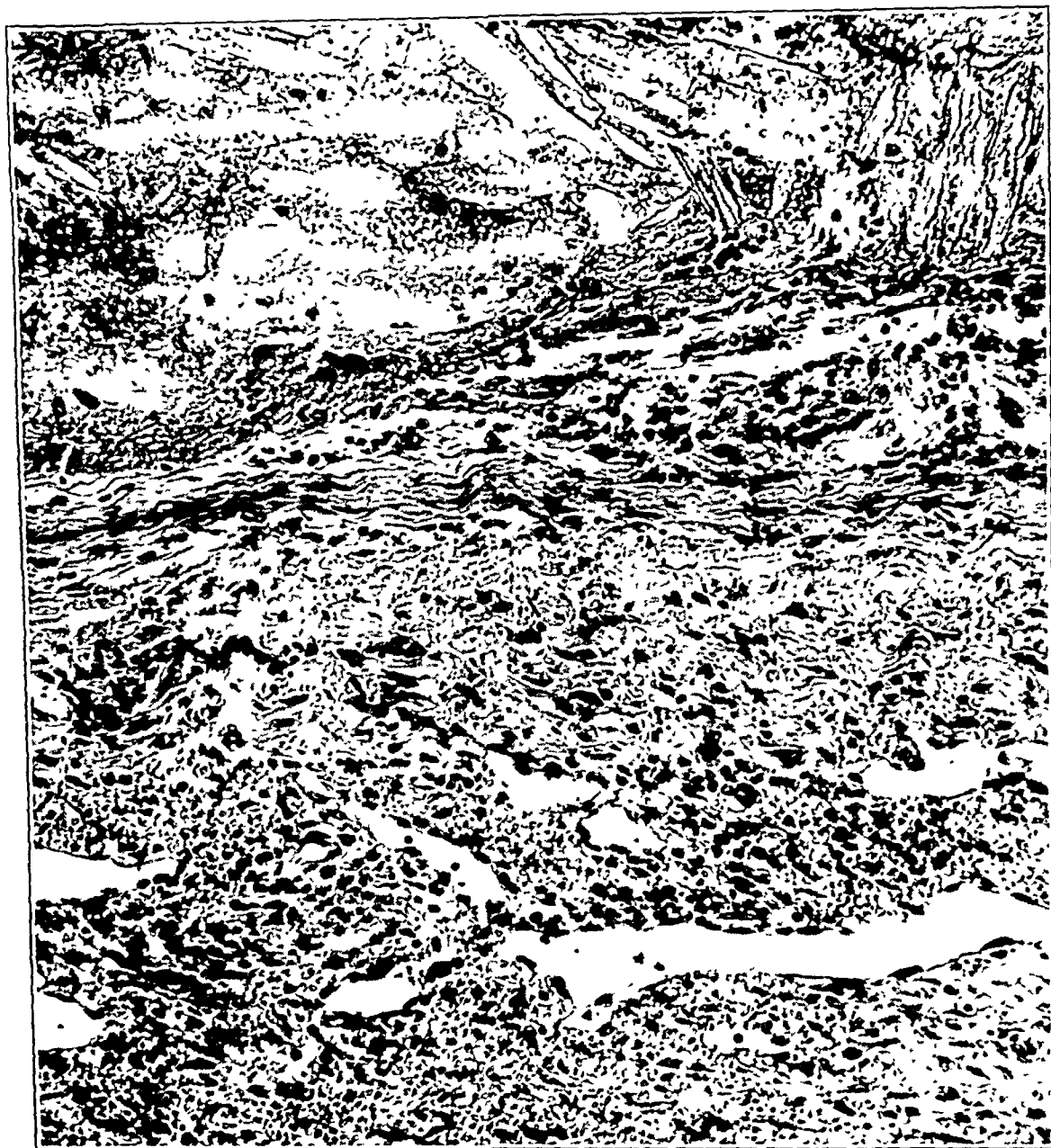
Fig. 1.—Photomicrograph of dura mater, one week after implantation of sulfathiazole (dog DP 12). Linear collections of crystals, with surrounding inflammatory reaction, appear in the upper portion. Extensive interstitial hemorrhage is seen in the fibroblastic tissue in the lower part. Hematoxylin and eosin; × 225.

Within a few hours of placement of any of the drugs a severe acute inflammatory response was noted in both the dura and the pia, giving way gradually to infiltration of plasma and round cells and fibrous and vascular reparative processes (fig. 4). With sulfanilamide the inflammatory reaction was mild, especially in the dura, and was of shorter duration, rarely being demonstrable in the dura after forty-eight hours. With the other two drugs active inflammation could be seen in the dura for two weeks and in the pia for as long as two months. It seemed to persist with greater severity after implantation of sulfadiazine.

TABLE 3.—Data on Experiments with Sulfathiazole

Type of Experiment	Dog No.	Amount of Drug per Kg. of Body Weight, Mg.	Duration of Life or Observation*	Convulsions	Maximum Drug Level in Cerebrospinal Fluid, Mg. per 100 Cc.	Maximum Drug Level in Blood, Mg. per 100 Cc.	Maximum Cell Count in Cerebrospinal Fluid	Gross: Drug Remaining	Gross: Subcortical Hemorrhage	Gross: Corticodural Adhesions	Dura: Drug Crystals	Dura: Acute or Subacute Inflammation	Dura: Interstitial Hemorrhage	Dura: Fibroplasia	Drug Crystals in Pia Mater	Acute or Subacute Leptomeningitis	Cortex: Subcortical Hemorrhage	Cortex: Proliferation of Astrocytes	Cortex: Proliferation of Oligodendrogliocytes	Cortex: Microglial Changes	Cortex: Degeneration of Neurons
1. Intravenously (sodium salt)	DP 22	50	30 hr. R	—	Trace	3.0	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
	DP 23	50	30 hr. R	—	Trace	4.4	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
2. By gastric tube	DP 26	50	30 hr. R	—	0.5	3.4	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
	DP 27	50	30 hr. R	—	0.7	5.3	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
3. Implanted on cortex	DP 6	66	18 hr. D	+++++	1.4	0.6	..	+++	—	—	++	++	+	—	+	+	—	—	—	—	—
	DP 3	66	24 hr. K	+++++	Trace	0.5	127	+++	—	—	+	+	—	—	+	++	—	—	—	—	—
	DP 4	66	24 hr. K	+	Trace	0.5	72	+++	—	—	++	++	+	+	+++	+++	++	—	—	—	+
	DP 2	66	18 hr. K	+++++	Trace	0.5	93	+++	—	—	—	++	+	+	++	++	++	—	—	—	+
	DP 5	66	48 hr. K	+++++	Trace	0.7	129	+++	—	++	+++	+++	++	—	+++	+++	—	—	—	—	++
	DP 10	66	48 hr. K	+++++	Trace	0.5	..	+++	—	++	++	+++	+++	+	+++	+++	—	—	—	—	++
	DP 39	66	72 hr. K	+++++	Trace	Trace	1,034	+++	—	+	+++	+++	+++	++	++	+++	—	+	+	+	++
	DP 11	66	1 wk. K	+++++	Trace	0.5	38	+++	—	++	+++	++	++	++	++	++	—	+	+	+	++
	DP 12	66	1 wk. K	+++	Trace	0.6	..	+++	—	+	+++	++	+	++	+	++	—	—	—	—	+
	DP 47	33	2 wk. K	+++	Trace	0.5	1,125	—	—	+++	—	+	—	++	—	++	—	—	—	—	+
	DP 48	33	2 wk. K	+++	Trace	0.5	—	—	—	+++	—	+++	+	++	—	+++	—	++	+	+	++
	DP 20	33	1 mo. K	+++++	Trace	Trace	43	—	+	+++	+	++	+	++	+	+	—	+++	+	+	+++
	DP 21	33	1 mo. K	—	Trace	Trace	40	—	+	+	+	++	—	+++	+	—	—	+	—	—	++
	DP 37	10	24 hr. K	—	0.5	Trace	..	++	—	+	+	++	++	—	—	++	+	—	—	—	—
	DP 38	10	24 hr. K	++	0.5	Trace	2,260	++	+	—	++	+++	+	—	+	+++	—	—	—	—	+
	DP 13	10	48 hr. K	—	Trace	0.5	93	+++	+	+	—	+++	++	—	—	+++	+	—	—	—	++
	DP 15	10	48 hr. K	—	0.6	Trace	76	++	+	++	—	++	+	—	—	++	+	—	—	—	++
	DP 29	10	3 days D	+++++	Trace	Trace	9	+	—	++	++	++	++	—	+	+	—	—	—	—	+
	DP 34	10	1 wk. K	—	Trace	Trace	8	—	—	+	+	—	—	+	—	—	—	—	—	+	—
	DP 35	10	1 wk. K	+++	Trace	Trace	35	—	—	+++	—	—	—	++	—	+	+	—	—	+	+
	DP 30	10	2 wk. K	—	Trace	Trace	..	—	—	++	—	—	—	++	—	++	+	—	—	—	—
	DP 31†	10	2 wk. K	—	Trace	Trace	6	—	—	+++	—	—	—	+++	—	—	+	—	—	—	+++
	DP 28	10	7 wk. K	—	Trace	Trace	7	—	—	+++	—	—	—	+++	—	—	+	++	++	++	++
	DP 36	10	2 mo. K	+++	Trace	Trace	10	+	—	+++	—	—	—	+++	—	+	+	+	+	+	+++
	DP 33	10	4 mo. R	—	Trace	Trace	10	—	+	—	—	—	—	—	—	—	—	—	—	+	+
	DP 32	10	6 mo. K	++	Trace	Trace	..	..	—	++	..	.	..	..	..	..	—	..	..	..	..

638

Group	No.	Dose	Time		Rating			Count	Rating
4. In area of cortical excision	DP 41	10	1 wk.	K	−	Trace	Trace	16	++
	DP 42	10	1 wk.	K	−	Trace	Trace	−	++
	DP 43	10	2 wk.	K	+	Trace	Trace	..	−
	DP 44	10	2 mo.	K	−	Trace	Trace	48	−
	DP 45	10	2 mo.	K	−	Trace	Trace	4	−
	DP 46	10	2 mo.	K	−	Trace	Trace		−
5. Epidurally (dura intact)	DP 55	66	24 hr.	K	−	..	0.5	..	+++
	DP 56	66	48 hr.	K	−	..	0.5	..	+++
	DP 57	66	1 wk.	K	−	..	0.6	..	++
	DP 58	66	1 wk.	K	−	..	0.5	..	++
6. Epidurally (0.5 cm. slit in dura)	DP 63	66	3 days	K	++++	0.5	0.7	34	+++
	DP 64	66	1 wk.	K	−	0.7	1.9	1,620	+
	DP 65	66	1 wk.	K	++	Trace	0.5	36	+
	DP 66	66	1 wk.	K	−	5.9	0.9	250	+
7. Epidurally (1 cm. slit in dura)	DP 61	66	48 hr.	K	+	Trace	0.5	11	+++
	DP 62	66	48 hr.	K	+	Trace	Trace	22	++++
	DP 59	66	1 wk.	K	+	Trace	0.5	364	−
	DP 60	66	1 wk.	K	+	Trace	0.6	58	+++
8. Cisternally (20% suspension of micro-crystals)	DP 67	2.5 Cc.	1 hr.	D	+++++	++++	0.5	..	++
	DP 68	2.5	1 hr.	D	+++++	++++	0.9	..	..
	DP 69	2.5	3 hr.	D	+++++	++++	1.0	..	++
	DP 70	2.5	6 hr.	D	+++++	+++++	1.3	..	..
9. Cisternally (2% suspension of microcrystals)	DP 71	2.5	3 hr.	D	+++++	+++++	0.6	..	++
	DP 72	2.5	4 hr.	D	+++++	+++++	0.9	..	++
	DP 74	2.5	4 days	D	+++++	60	0.8	1,250	−
	DP 73	2.5	2 wk.	K	+	74	0.5	684	−

* See footnote to table 1.
† Animal possibly infected; see text.

639

TABLE 4.—*Data on Experiments with Sulfadiazine*

Type of Experiment	Dog No.	Amount of Drug per Kg. of Body Weight, Mg.	Duration of Life or Observation*	Clinical Observations				Gross Pathologic Changes			Microscopic Pathologic Changes							Cerebral Cortex			
				Convulsions	Maximum Drug Level in Cerebrospinal Fluid, Mg. per 100 Cc.	Maximum Drug Level in Blood, Mg. per 100 Cc.	Maximum Cell Count in Cerebrospinal Fluid	Drug Remaining	Subcortical Hemorrhage	Corticodural Adhesions	Drug Crystals (Dura Mater)	Acute or Subacute Inflammation (Dura Mater)	Interstitial Hemorrhage (Dura Mater)	Fibroplasia (Dura Mater)	Drug Crystals in Pia Mater	Acute or Subacute Leptomeningitis	Subcortical Hemorrhage	Proliferation of Astrocytes	Proliferation of Oligodendrogliocytes	Microglial Changes	Degeneration of Neurons
1. Intravenously (sodium salt)	RJ 13	50	30 hr. R	—	2.1	6.5	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
	RJ 14	50	30 hr. R	—	3.9	8.1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
2. Orally	RJ 17	50	53 hr. R	—	3.6	5.4	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
	RJ 18	50	53 hr. R	—	2.4	3.7	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
	RJ 28	50	72 hr. R	—	1.5	2.1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
3. On cortex	RJ 5	66	21 hr. K	—	0.7	0.9	4	+++	—	++	—	++	++	—	—	++	+	—	—	—	—
	RJ 6	66	21 hr. K	—	2.2	0.6	11	+++	+	+	—	+++	++	—	—	+++	—	—	—	+	—
	RJ 2	66	18 hr. K	—	0.8	Trace	23	+++	++	+++	—	+++	—	—	—	++	+	—	—	—	—
	RJ 3	66	48 hr. K	—	Trace	0.5	17	+++	++	++	—	—	—	++	—	+	+	—	—	—	—
	RJ 1	66	1 wk. K	—	Trace	0.6	2	+++	—	++	—	+	+	++	—	+++	—	++	—	—	++
	RJ 4	66	1 wk. K	—	0.5	0.6	4	+++	—	++	—	+	—	+++	+	+++	—	++	—	—	++
	RJ 7	10	2 wk. K	—	Trace	Trace	1	—	—	++++	—	—	—	++	—	+++	+	++	—	—	++
	RJ 8	10	2 wk. K	—	Trace	Trace	..	—	—	++++	—	+	—	+++	—	+++	+	+++	—	+	++
	RJ 9	10	2 mo. K	—	Trace	Trace	5	—	—	++++	—	++	—	+++	—	+++	+	+++	—	—	++
	RJ 10	10	2 mo. K	—	Trace	Trace	30	—	—	++++	—	—	—	+++	—	+++	—	—	—	—	—
	RJ 11	10	4 mo. D	—	Trace	Trace	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	RJ 12	10	6 mo. K	—	Trace	Trace	13	—	—	++	—	+	—	++	+	:+	—	:+	—	:+	:—
4. In area of cortical excision	RJ 21	10	1 wk. K	—	Trace	Trace	926	+	++	++	—	++	—	++	—	++	++	++	++	+++	++
	RJ 19	10	2 wk. K	—	Trace	Trace	6	—	—	+++	—	++	—	+++	—	++	+++	+	++	++	++
	RJ 20	10	2 wk. K	—	0.5	0.5	0	—	—	+++	—	—	—	—	—	++	++	—	—	—	+++
	RJ 15	10	2 mo. K	—	Trace	Trace	27	—	—	+++	+	:+	—	:+	—	++	+++	:+	:+	:+	+++
	RJ 16	10	2 mo. K	—	Trace	Trace	23	—	—	+++	—	:+	—	:+	—	++	+++	+++	+++	++	++
5. Cisternally (20% microcrystalline suspension)	RJ 23	2.5 Cc.	4 hr. D	D++++	60.0	1.2	..	—	—	—	—	+++	—	—	—	++	+++	—	—	—	—
	RJ 22	2.5	2 wk. K	—	138.0	2.0	..	—	—	—	—	+++	—	—	—	+++	+++	—	—	—	—
	RJ 24	2.5	2 wk. K	—	136.0	1.8	..	—	—	—	—	:+	—	—	—	++	:+	—	—	—	—
	RJ 25	2.5	2 wk. K	—	98.0	1.5	..	—	—	—	:—	:+	—	:+	—	+++	:+	—	—	—	—
	RJ 26	2.5	2 wk. K	—	111.0	2.3	..	—	—	—	—	—	—	—	—	+++	+++	—	—	—	—
	RJ 27	2.5	2 wk. K	—	111.0	1.6	..	—	—	+	—	—	—	—	:+	+++	—	—	—	—	—

* See footnote to table 1.

640

The most striking change was the remarkable stimulation of growth of fibrous tissue in the dura mater. This was first seen in animals killed one week after application of any of the drugs. With sulfanilamide, it consisted of an exuberant, but relatively typical, reparative process, characterized by growth of fibroblasts and young vessels and, later, by the laying down of dense elastic tissue. Although more extensive, it was not unlike the healing process demonstrated in the control series of experiments and was no more marked than in the experiments with kaolin.

Fig. 2.—Photomicrograph of dura, showing a mass of rapidly proliferating fibroblasts one month after implantation of sulfathiazole (dog DP 20). Note the wild, almost neoplastic, growth. Hematoxylin and eosin; × 225.

On the other hand, both sulfathiazole and sulfadiazine produced extensive hyperplasia of primitive fibroblastic tissue, which gave the appearance of being neoplastic. Masses and streams of elongated cells were heaped up on both the inner and the outer surface of the dura and sometimes seemed to invade it. Mitotic figures were not infrequent. Collagen and reticulin formed a fine, but exuberant, intercellular network, as seen in aniline blue–orange G, phosphotungstic acid

hematoxylin and Perdrau preparations (figs. 2 and 3). This fibroplasia was more prominent with sulfadiazine than with sulfathiazole.

Similar fibroblastic stimulation was not seen in the pia mater, except for moderate fibrosis in experiments of longer duration with all of the drugs.

In all experiments of this type, there was pronounced vascular engorgement in the entire region involved, including the dura, pia and cortex and involving arteries, veins and capillaries. In the dura, interstitial hemorrhage was almost

Fig 3—Photomicrograph of dura, showing the heavy network of reticulin two weeks after implantation of sulfadiazine (dog RJ 8). Perdrau impregnation for reticulin, × 120.

invariably seen when the animal was killed within one week (fig. 1). This was most marked after the implantation of sulfathiazole, as was hemorihage into the cerebral tissue, which often extended 1 or 2 cm. beneath the coitex and varied from grossly visible hematomas to microscopic extravasations of a few red blood cells.

By the end of the first week, and progressing slowly thereafter, changes in the cellular constituents of the cortex appeared. Nerve cells showed pyknosis of nuclei, vacuolization, granular breakdown of the Nissl substance and abnormal

cellular shapes. Such neuronal changes were seldom extensive or far advanced, except in a few instances in which small focal areas of subcortical necrosis were seen. Such areas were usually contiguous to penetrating vessels about which a pronounced inflammatory process existed. Proliferation of the oligodendroglia was roughly proportional to, and was never encountered without, neuronal degeneration.

The microglia cells showed varying degrees of change, from simple swelling and diminution of protoplasmic cellular extensions, on the one hand, to formation.

Fig. 4.—Mild, subacute inflammatory reaction in the pia mater and underlying cortex one week after implantation of sulfanilamide (dog WM 1). Hematoxylin and eosin; × 225.

of masses of phagocytic compound granular corpuscles, on the other (fig. 9 A and B). Such changes tended to parallel the amount of hemorrhage and necrosis which was present.[3]

These evidences of degeneration were distinctly more frequent in experiments in which sulfathiazole was employed (neuronal changes in 75 per cent of experi-

3. In 1 experiment (DP 31), extensive acute inflammation and necrosis were suspected of being due to infection, but since cultures were sterile, the experiment is included.

ments with sulfathiazole lasting longer than twenty-four hours, as compared with 60 per cent in experiments with sulfanilamide and 33 per cent in experiments with sulfadiazine).

During this same period (largely after the first week) two types of astrocytic changes were seen. In relation to the uncommon zones of focal necrosis, the astrocytes were swollen, morphologically variable and almost without glial fibrillae (figs. 5 and 7). On the other hand, in the subpial regions and the adjacent cortical layers there was typical fibrillary gliosis. The latter glial change was never far advanced in the experiments with sulfanilamide, was advanced in many experiments with sulfathiazole and was almost invariably extreme in the experiments with sulfadiazine.
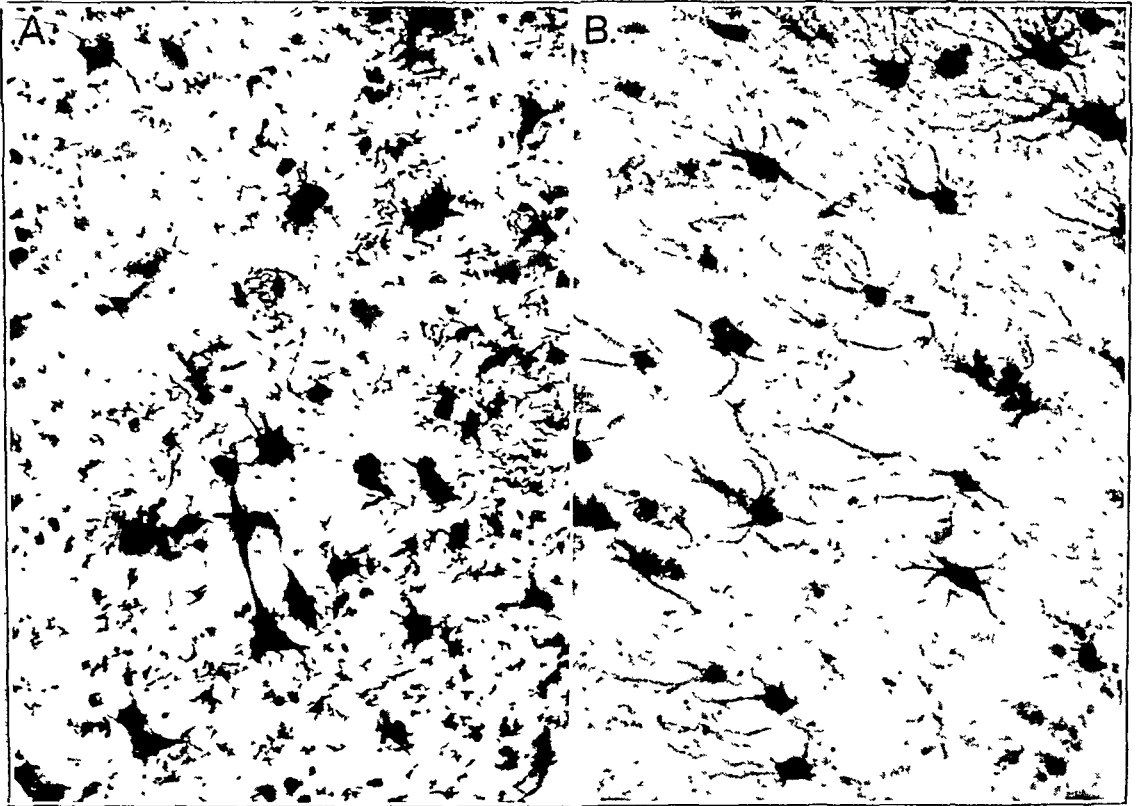
Fig. 5—Early changes in the astrocytes one week after placement of sulfanilamide (dog WM 2). The two photomicrographs are from areas 1 mm. apart in the same section. (*A*) The astrocytes are swollen and distorted at the edge of an area of necrosis. Glial fibrillae are almost absent. (*B*) In the adjacent area the cells are still swollen, but fibrillae are well formed and the process of formation of a glial scar has begun. Ramón y Cajal's gold chloride-mercury bichloride method; × 277.

D. Implantation of Sulfonamide Compounds in an Area of Cortical Excision.— In this series, 10 mg. of the drug per kilogram of body weight was placed in a cuplike cavity, about 1 cm. in diameter, from which cortical tissue had been excised. Animals were killed after intervals of one week to two months.

One animal with sulfathiazole had one convulsion. No other convulsions were observed in any of the experiments, nor were other significant clinical changes noted. Only slight pleocytosis was produced in most of the experiments.

Necropsy revealed that sulfathiazole was grossly visible through the first week. Sulfanilamide was not seen at all, and only a minute quantity of sulfadiazine was detected at the end of one week in 1 animal.

Histologically, the reactive changes already described were present, in addition to the necrosis, hemorrhage and reparative processes resulting from the operative trauma. It was our distinct impression that the intracerebral hemorrhage and
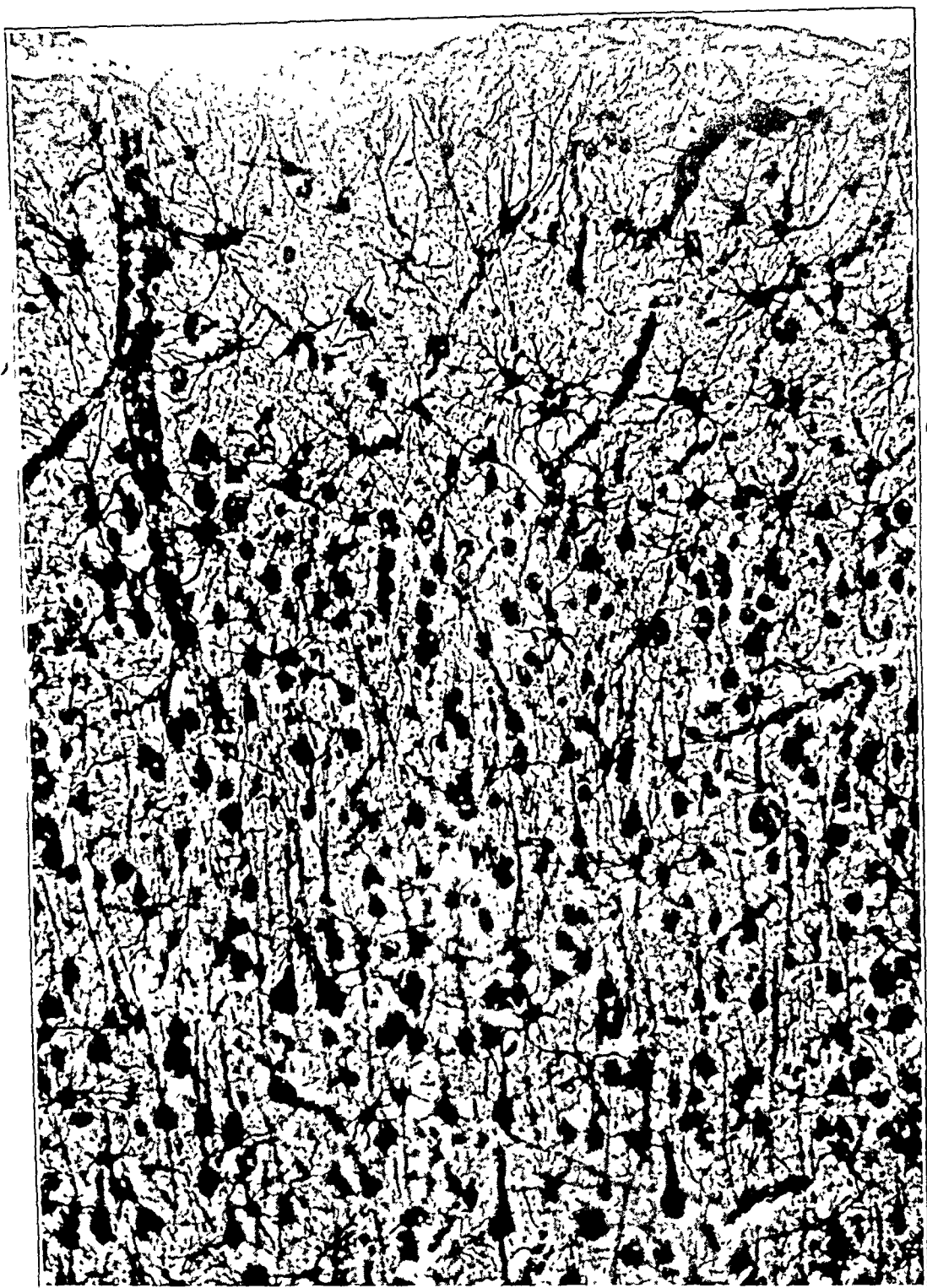
Fig. 6.—Section of cortex, showing superficial gliosis in a control experiment two months after operation (dog DP 10). Although the astrocytes are proliferating among the nerve cells, the essential normal structure is preserved. Silver carbonate method; × 225.

vascular dilatation were more extensive and more distantly encountered with sulfathiazole than with the other drugs.

E. Epidural Implantation of Sulfathiazole (table 3 [experiments 4-9]).—Because of convulsions resulting from the intradural placement of sulfathiazole, this drug

was placed on the outer surface of the dura in three groups of experiments. The dura was left intact in one group and was incised by linear incisions of 0.5 and 1 cm., respectively in the other two groups. The duration of the experiments varied from twenty-four hours to one week.
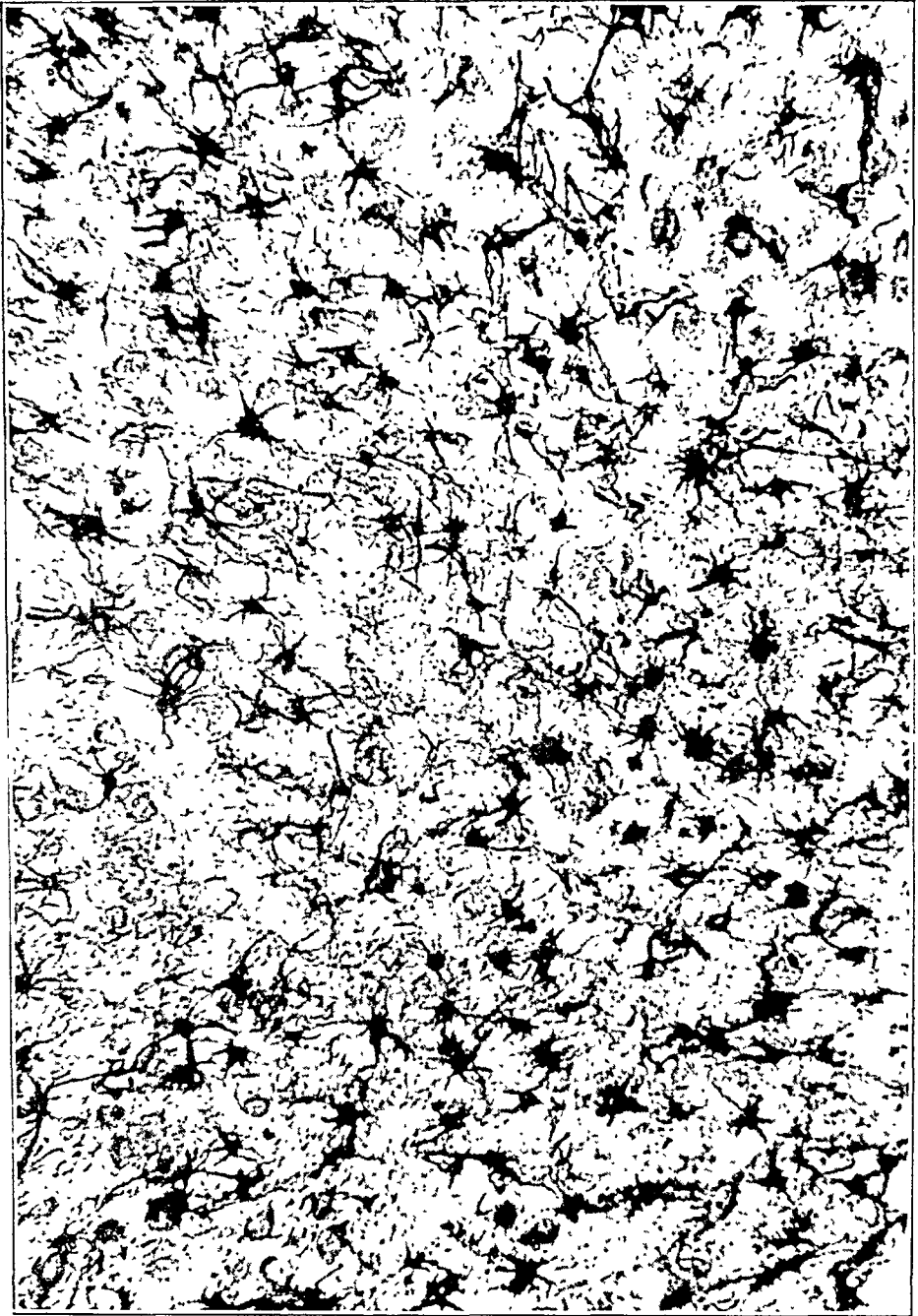
Fig. 7.—Dense glial scar in the cortex six months after placement of sulfathiazole (dog DP 32). Ramón y Cajal's gold chloride–mercury bichloride method; × 225.

With the dura intact, no convulsions were observed. With the dura incised 0.5 cm., 2 of 4 animals had convulsions, and with a 1 cm. incision in the dura, all 4 animals had convulsions. Exception for violent status epilepticus in 1 dog

(DP 63), the seizures were neither as severe nor as frequent as when the drug was placed inside the dura.

The drug persisted grossly until necropsy in all but 1 of the 12 experiments. Microscopically, crystals were seen in or attached to the dura in most experiments, and in 1 animal (DP 65) a large mass of crystals lay in the pia mater.
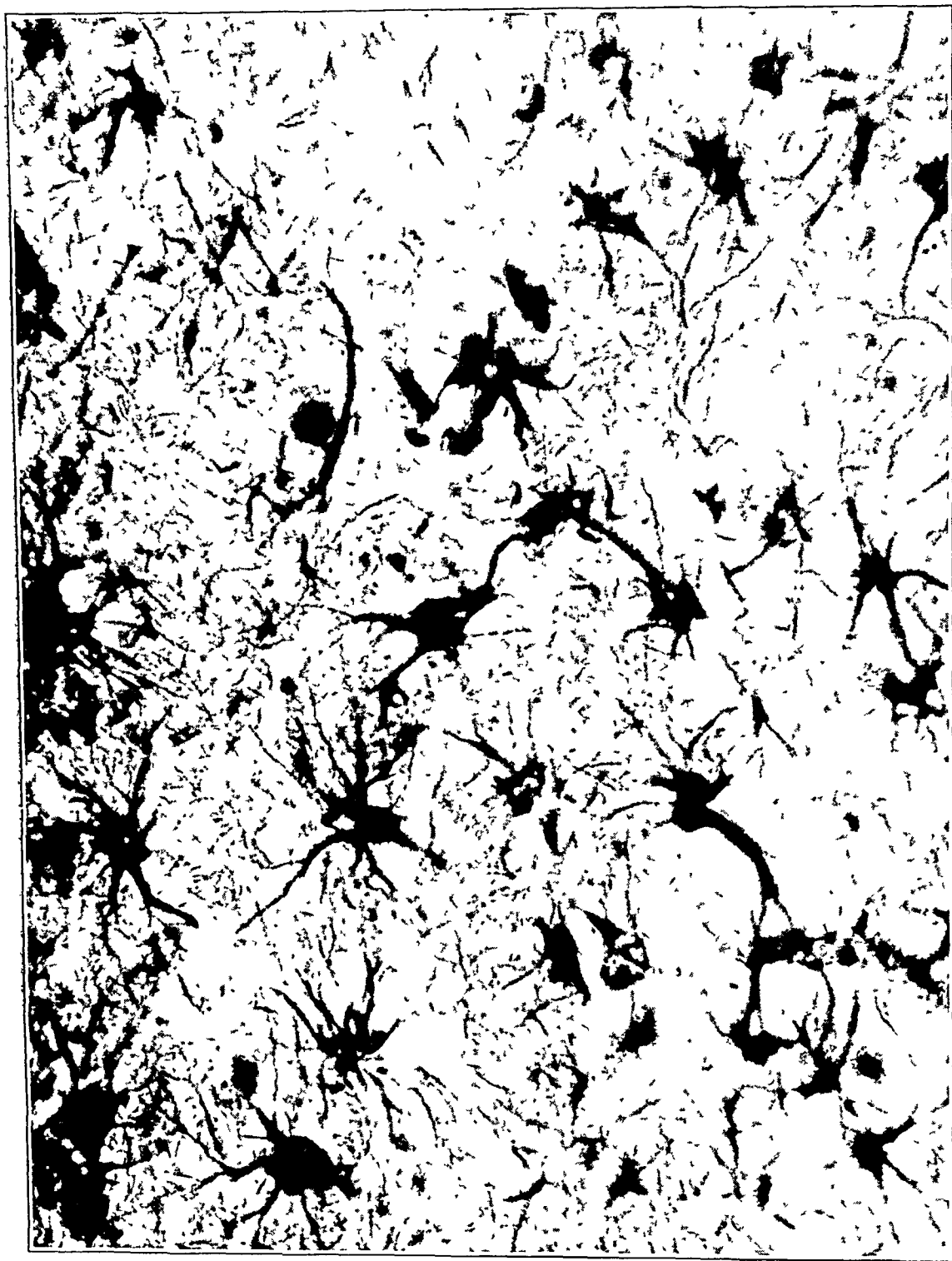
Fig. 8.—Heavy gliosis six months after implantation of sulfadiazine (dog RJ 12). No normal cellular elements remain. Ramón y Cajal's gold chloride–mercury bichloride method; × 500.

Even with the dura intact, leptomeningitis was present in 3 of 4 animals, and it was invariably present if the dura had been incised. The same vascular and

cellular changes in the brain previously described were present with lesser frequency and to a lesser degree.

F. Cisternal Injection of Microcrystalline Suspensions of Sulfathiazole and Sulfadiazine.—Chambers, Harris, Schumann and Ferguson[4] reported the use of microcrystals of sulfathiazole produced by precipitation in a medium agitated by
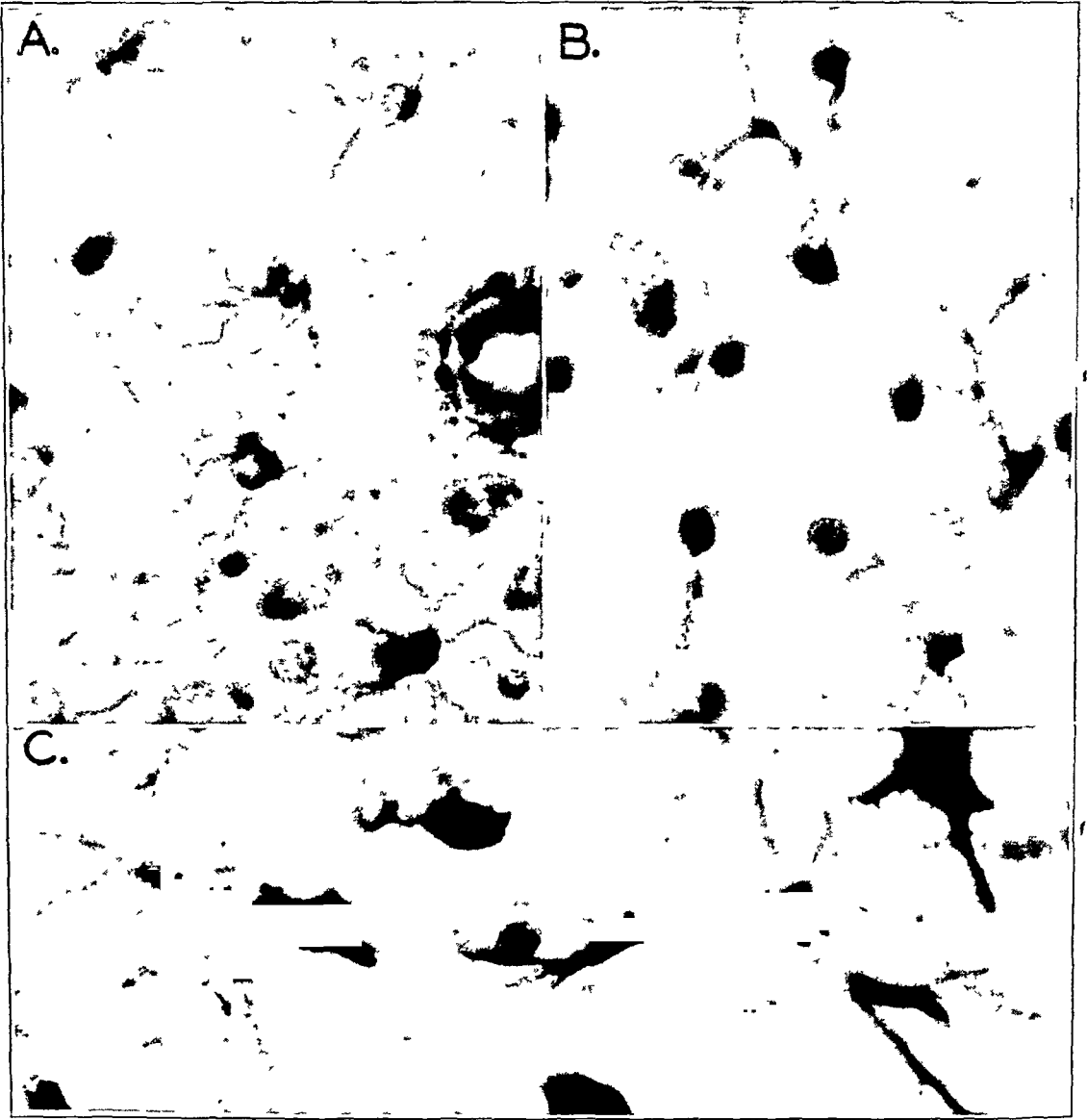
Fig. 9.—Changes in microglia and oligodendroglia. *A,* metamorphosis of microgliocytes two weeks after implantation of sulfathiazole (dog DP 31). The nuclei and cell bodies are in various stages of swelling. Several cells have completed the change, lost their processes and become compound granular corpuscles. Penfield's combined method; $\times$ 625. *B,* slight microglial change two weeks after sulfanilamide was placed in an area of cortical excision (dog WM 22). Penfield's combined method; $\times$ 1,000. *C,* swollen, distorted oligodendrogliocytes one week after placement of sulfadiazine (dog RJ 8). Note the enlarged, eccentric nuclei. Penfield's combined method; $\times$ 1,200.

4. Chambers, L. A.; Harris, T. N.; Schumann, F., and Ferguson, L. K.: The Use of Microcrystals of Sulfathiazole in Surgery, J. A. M. A. **119**:324 (May 23) 1942.

sonic waves. Suspensions of such microcrystals may be injected through relatively fine needles.

In our experiments, 2.5 cc. of a 20 per cent suspension of sulfathiazole or sulfadiazine or a 2 per cent suspension of sulfathiazole was injected into the cisterna magna, after removal of an equal volume of cerebrospinal fluid (tables 3 [experiments 4-9] and 4).

After injection of sulfathiazole in either a 20 or a 2 per cent suspension, violent convulsions invariably occurred. They terminated fatally within one to six hours in 6 experiments and in four days in another. In experiment 8 (DP 73) the dog had only mild facial twitching for a few hours and survived. Extreme salivation persisted, however, until the termination of the experiment, at the end of two weeks.

After injection of a suspension of microcrystalline sulfadiazine, fatal convulsions occurred in only 1 of 6 experiments, the animals in the remaining 5 experiments having no convulsions and being allowed to live two weeks.

With sulfathiazole, the dura was normal in the 2 instances in which it was examined, and there was mild leptomeningitis in only 2 of the 6 animals in which sections were made of the brain. One of these sections showed masses of the crystals in the pia and in the superficial layers of the cerebral cortex. Crystals were also seen within the lumens of small subpial vessels in two sections.

With sulfadiazine, both the dura and the pia mater showed more severe inflammatory reaction. This was present over the cerebral hemispheres, as well as at the base of the brain.

There was no microscopic evidence of cerebral injury except for subcortical bleeding in 1 of the experiments with sulfathiazole (DP 72).

COMMENT

The production of convulsions by placement of sulfathiazole on the cortex was discussed in the preliminary report[1] already referred to. Additional experiments described here indicate that these seizures may be produced when the drug is placed extradurally, providing a very small opening in the dura exists. In support of this is the clinical case of Naffziger[5] in which sulfathiazole was placed in a frontal craniotomy wound after suture of the dura. The patient went into status epilepticus, which lasted many hours. Watt and Alexander[6] reported a similar case.

The violence and the fatal outcome of the seizures which followed the cisternal injection of suspensions of microcrystalline sulfathiazole present no obvious explanation. It is possible that a direct toxic effect on the medulla was produced. Further, the smaller crystals may more readily have obtained access to subcortical neurons, as suggested by the microcrystals of sulfathiazole seen in the cortex in 1 experiment.

It is notable that convulsions were never produced when sulfathiazole was placed in an excavation in the cerebral hemisphere. Seemingly, the effect of the drug must be exerted on the intact cortex in order to induce convulsions.

That convulsions were not produced in the experiments with kaolin, and rarely with sulfanilamide or sulfadiazine, indicates that the effect of sulfathiazole is specific. As already pointed out,[1] the epileptogenic effect of sulfathiazole has also been demonstrated in rabbits, cats and human beings and was clearly shown in the

5. Naffziger, H. A.: Personal communication to the authors.

6. Watt, A. C., and Alexander, G. L.: Epilepsy Following Application of Sulfathiazole Near the Brain, Lancet **1**:493 (April 25) 1942.

experiments of Watt and Alexander [6] on dogs and cats and those of Jasper, Cone, Pudenz and Bennett [7] on monkeys.

It is not surprising that Hurteau [8] observed no convulsions in his experiments, since he placed sulfathiazole, as well as other drugs, in an area of cortical excision, as was done in experiments DP 41 to DP 46 in our series. Botterell, Carmichael and Cone [9] recorded no convulsions after implanting sulfanilamide and sulfapyridine in areas of cortical excision, but they did not employ sulfathiazole. Ingraham and Alexander [10] did not observe convulsions after application of sulfathiazole to the brains of 3 cats.

Except for the production of convulsions with sulfathiazole, it is of interest that the effects of the several drugs on the brain and its coverings were qualitatively the same in our experiments. Indeed, it must not be forgotten that, at least in the meninges, many of the changes were qualitatively identical in the experiments in which no drug was employed.

Significant quantitative differences were observed, however. Inflammatory, destructive and reparative processes were distinctly less extensive with sulfanilamide than with the other two drugs but were more advanced than in the control animals. The extent of dural and subcortical hemorrhage was greatest with sulfathiazole.

The histologic changes observed by us were essentially similar to those recorded by Hurteau [8] and by Botterell, Carmichael and Cone.[9] Hurteau stated, however, that the reaction to sulfadiazine observed "did not exceed that seen in similar wounds without the application of chemicals." In our experiments, the extensive fibroplasia in the dura, the inflammation in the leptomeninges, the vascular engorgement and hemorrhage, the conspicuous microglial changes and the gliosis were far greater when the drugs were employed.

Russell and Falconer [11] placed several sulfonamide compounds on and (by injection) in the rabbit brain. The principal effect observed by them was a conspicuous foreign body reaction.

It should be noted that no morphologic alteration which could be related to the production of convulsions could be demonstrated. The type of neuronal degeneration observed after implantation of sulfathiazole was identical with that associated with the other drugs.

It must be emphasized that the observations recorded in this paper do not constitute or justify a condemnation of the use of the sulfonamide compounds in the therapy of intracranial infections. These experiments do show, however, that these drugs are not entirely innocuous agents and that they should be employed with caution and with critical judgment. Moreover, it is our belief that sulfathiazole should never be used in cranial wounds in which the dura mater is or has been open.

Our experiments are not comparable to the best clinical practice at present because of the amounts of the drugs employed. It is surprising, however, how

7. Jasper, H.; Cone, W.; Pudenz, R., and Bennett, T.: The Electroencephalograms of Monkeys Following the Application of Microcrystalline Sulfonamides to the Brain, Surg., Gynec. & Obst. **76**:599 (May) 1943.

8. Hurteau, E. F.: The Intracranial Use of the Sulfonamides: Experimental Study of the Histology and Rate of Absorption, Canad. M. A. J. **44**:352 (April) 1941; The Intracranial Use of Sulfadiazine: Experimental Study of the Histology and Rate of Absorption, ibid. **46**:15 (Jan.) 1942.

9. Botterell, E. H.; Carmichael, E. A., and Cone, W. V.: Sulfanilamide and Sulfapyridine in Experimental Cerebral Wounds, J. Neurol. & Psychiat. **4**:163 (July-Oct.) 1941.

10. Ingraham, F. D., and Alexander, E.: Experimental Application of Sulfonamide Drugs to the Cerebral Cortex, New England J. Med. **227**:374 (Sept. 3) 1942.

11. Russell, D., and Falconer, M. A.: Local Effects of Sulphonamides on the Rabbit's Brain, Lancet **2**:100 (July 27) 1940.

frequently one reads, "the wound was filled with sulfanilamide." Our results indicate that the reaction increases proportionately with the amount of the drug and suggest that the smallest effective amount of the drug should be employed. Data pertaining to the minimal effective dose will be presented in reports dealing with the treatment of experimental intracranial infections.

SUMMARY

In this paper 115 experiments are reported in which sulfanilamide, sulfathiazole or sulfadiazine was implanted intracranially by various methods and in various amounts.

Important clinical results were the production of convulsions by sulfathiazole (when placed on the intact cerebral cortex) and of pleocytosis by all three of the drugs.

Significant pathologic effects were: (1) immediate acute pachymeningitis and leptomeningitis, with corresponding subacute or chronic inflammation in the later stages; (2) marked fibroplasia in the dura; (3) conspicuous gliosis in the cortex, and (4) varying degrees of neuronal degeneration, proliferation of oligodendrogliocytes and metamorphosis of microglia cells.

All reactions were least extensive when sulfanilamide was employed and increased with all the drugs when the dose was increased.

These experiments do not indicate that the effects of sulfanilamide and sulfadiazine are sufficiently harmful to contraindicate their critical use in the therapy of intracranial infections. They suggest that sulfathiazole should never be employed in a cranial wound in which there is an opening in the dura.

Vanderbilt University Hospital.

ELECTRIC CONVULSIVE THERAPY, WITH EMPHASIS ON IMPORTANCE OF ADEQUATE TREATMENT

LOTHAR B. KALINOWSKY, M.D.

NEW YORK

The value of shock treatment of mental disease is still disputed. At present electric convulsive therapy is probably the most widely used method. With some disorders indiscriminate use is favored because of its simplicity, whereas with others inadequate application is responsible for failures. This paper represents an endeavor to give indications for the application of this therapy, on the basis of experience with more than 1,500 patients treated by the same physician in two parallel series: the one, at the New York State Psychiatric Institute and Hospital, and the other, representing institutional material, at the Pilgrim State Hospital.

Discrepancies in reports on the value of shock treatment demand a clear definition of the material from which conclusions are drawn. Statistical work on diagnostically doubtful and borderline cases is valueless at the present experimental stage. There are, however, clearcut cases of the various major psychoses in which disagreement as to diagnosis will be minimal. This "nuclear group," representing the classic textbook descriptions of the principal disorders, is found among patients committed to institutions for mental disease, rather than in the clinical material of research centers. Statistical evaluation is directed mainly toward results for such institutional patients as those listed in tables 1 and 2, not only because these patients represent to a large extent clearcut psychoses but because they were sufficiently ill to be committed to an institution. Thus, the decision with regard to the degree of improvement after shock therapy was made not by the treating physician, who might have been considered biased, but by the staff of the institution. Patients with borderline psychoses were not included in these groups. The importance, and perhaps even the greater frequency, of atypical cases of the major psychoses is fully realized, but the value of new and disputed procedures of treatment must be examined first on the basis of a homogeneous group of patients, on the diagnosis of whose disease most psychiatrists can agree.

TECHNIC AND APPLICATION

The present suggestions for variation in application of electric convulsive therapy in management of the different psychoses are based on empiric experience with the large material which was treated. In both hospitals the Rahm instrument was used.

Since the technic of Cerletti and Bini is accepted in its essentials by most workers, it will not be described again here; only a few points will be discussed.

Preliminary measurement of resistance is superfluous and of no help in determination of the required voltage. There is no relation of practical value between the reading of the tissue resistance and the necessary amount of current; high and low resistances determined for the same patient on different days do not cause noticeable differences in the voltage needed for a convulsion.

It has been asked whether, in case one fails to obtain a convulsion, the current or the time of exposure ought to be increased. Both adjustments are possible, although animal experiments have shown that the range of safety is wider when the intensity of the current

is increased.[1] I cannot fully corroborate the statement[2] that doubling the time reduces by half the necessary current.

Subconvulsive treatments are of little value and should be avoided. A series of patients was treated[3] by production of the petit mal response alone. The poor results of this procedure, as compared with the good effects of a later course of treatments of the same patients by induction of grand mal convulsions, have shown that production of major convulsions is necessary. Personal communications from many workers have indicated that often too great a number of nonconvulsive applications is interspersed through a course of electric shock treatments; such a procedure leads to unsatisfactory results. Reluctance to increase the current sufficiently after a minor seizure may produce a repetition of the nonconvulsive response, for minor seizures, without motor discharge, like convulsions, heighten the convulsive threshold.

A generalized seizure with each application is best obtained with a current of a strength which is slightly higher than necessary. There is no evidence that the danger of the method lies in the strength of the current itself. A strong current does not prolong the period of apnea; cardiovascular symptoms were seen more often with abortive seizures than with immediate convulsions. On the other hand, an unnecessarily strong current does not increase the strength or the duration of the muscular discharge. Moreover, a repetition of the application after a nonconvulsive response occasionally produces vasomotor and respiratory distress. A simple procedure makes it possible to avoid subconvulsive responses altogether. Whenever an application does not lead to an immediate convulsion, a second stimulus with a current of the same strength, or possibly one increased by 10 volts, is applied about five seconds later. Thus, the operator repeats the stimulus without waiting on the chance that a delayed convulsion may still occur. No untoward effect of any kind has been observed, even if the stimulus is repeated twice. For the first treatment, the worker should use a strength of current which, with his particular machine, produces an immediate convulsion in a fair proportion of subjects. Generally it can be stated that young male patients require the weakest current and old female patients the strongest.

Treatments are usually given three times a week. Daily treatments hasten the confusional state, which some workers consider necessary for good results. A small series of patients whom we treated with daily applications did not show better therapeutic effects, but there are some indications for more frequent treatments. Treatment days with 2, or even 3, convulsions each day were found to be useful in the breaking up of an otherwise inaccessible manic excitement. Furthermore, therapy of new patients in deep stupor, or in exhausting states of excitement, is started with 4 convulsive treatments, given on two subsequent days, 2 convulsions being produced each day one-half hour apart. In this way, the breaking up of such conditions is achieved in twenty-four hours, instead of eight or ten days. Such a procedure is surprisingly well tolerated, even by emaciated patients, perhaps because their muscular discharge during a seizure is particularly weak. With disturbed patients suffering from severe psychotic exhaustion, as well as with patients who present feeding problems, such intense treatment may be life saving.

The various points thus outlined have in common the principle of intensive treatment. Half-hearted application of any shock method means inadequate treatment and constitutes one of the chief reasons for failure. The insufficient therapeutic effects of light or medium hypoglycemic states in insulin treatment and of subconvulsive responses in electric shock and metrazol therapy make it a foregone conclusion that in all methods something which occurs in the brain only during deep coma brings about the response. One of the advantages of electric convulsive therapy is that the convulsive coma not only is easily obtained but is equally deep in each treatment, regardless of the skill of the therapeutist. The only requirement is that a convulsion be secured with each treatment and that the application of convulsions be continued for a sufficient length of time. This is particularly important in the treatment of schizophrenia.

INDICATIONS FOR THERAPY

A survey of my material leads to rather definite indications for therapy. Only brief comment will be made on those diseases with respect to the treatment of which most workers in this field agree; in the case of schizophrenia, for which the

1. Bini, L.: La tecnica e le manifestazioni dell'elettroshock, Riv. sper. di freniat. **64:** 361, 1940.

2. Hemphill, R. E., and Walter, W. G.: The Treatment of Mental Disorders by Electrically Induced Convulsions, J. Ment. Sc. **87:**256, 1941.

3. Kalinowsky, L.; Barrera, S. E., and Horwitz, W. A.: The "Petit Mal" Response in Electric Shock Therapy, Am. J. Psychiat. **98:**708, 1942.

reports on the value of this treatment are entirely in disagreement, the probable reasons will be discussed. The therapeutic indications in the following paragraphs are illustrated by the material from the Pilgrim State Hospital, presented in tables 1 and 2.

Manic-Depressive Psychoses.—Accord exists regarding the results with manic-depressive psychoses. The majority of patients in the depressed phase can be treated successfully; the incidence of remissions in most reports varies from 80 to 90 per cent. For acute manic syndromes my own results, poor in the earlier cases, are now as good as those for the depressive phase, but the usual number of 8 or 10 treatments as given for depressions, is not sufficient to maintain improvement in manic patients. The necessity for induction of 20, or even more, convulsions in some manic patients led us to apply more intensive treatment by means of 2 or 3 convulsions daily. Since this method is now used routinely, severe manic

TABLE 1.—*Results of Electric Convulsive Therapy in Two Hundred Patients with Affective Disorders*

Type of Psychosis	Total No.	Patients Recovered and Much Improved	Patients Improved	Patients Unimproved
Manic-depressive psychosis (depressed)	60	52 (86.6%)	4 (6.7%)	4 (6.7%)
Manic-depressive psychosis (manic)	32	27 (84.4%)	3 (9.4%)	2 (6.2%)
Involutional melancholia	76	66 (86.9%)	8 (10.5%)	2 (2.6%)
Involutional paranoia	32	14 (43.7%)	8 (25%)	10 (31.3%)
Total	200	159	23	18

TABLE 2.—*Results of Electric Convulsive Therapy in Two Hundred and Seventy-Five Patients with Acute Schizophrenia*

Duration of Illness	Total No.	Patients Recovered and Much Improved	Patients Improved	Patients Unimproved
Less than 6 months	60	41 (68.3%)	13 (21.7%)	6 (10%)
6 months to 2 years	82	34 (41.5%)	24 (29.3%)	24 (29.3%)
More than 2 years	87	8 (9.2%)	36 (41.4%)	43 (49.4%)
Long standing with previous remissions	46	26 (56.5%)	10 (21.7%)	10 (21.7%)
Total	275	109	83	83

excitements are usually broken up by a course of 5 or 6 convulsions, instead of 20 or more. Treatment of a patient in the manic phase will occasionally cause a shift to a depression and vice versa; in such instances continuation of treatment is necessary. However, the slight hypomanic reaction sometimes seen after treatment of a depression fades spontaneously and does not indicate further therapy. Patients with cyclic states, with constant shifting from one phase to the other, did not benefit from the therapy.

At present it appears impossible to prevent, or even to diminish, the number of attacks in patients with manic-depressive psychoses, but that it is possible to cut short a depression, with all its attendant suffering for the patient and his family, is recognized as representing great progress. Usually the remission takes place after the third or fourth treatment. It seems advisable to stabilize the result with at least a few additional treatments, although the necessity for such procedure is not proved. Additional psychotherapy was given in one of our series but was omitted with the patients represented in the tables. The favorable results for this group of institutional patients with severe psychoses indicate that psychotherapy following shock treatment is not imperative for acutely psychotic patients.

Involutional Psychoses.—Patients with pure involutional melancholia showed the same rate of remission as patients with depressions of the manic-depressive type. A longer duration of this disorder did not interfere with a successful outcome. There is no more convincing evidence of the effectiveness of convulsive treatment than the improvement in patients, long tube fed and mute, who after less than 5 convulsions talk and resume normal behavior.

The first patients to be mentioned for whom poorer results were obtained were those with the paranoid type of involutional psychosis. For these patients, as well as for patients presenting involutional depressions mixed with paranoid symptoms, results were not at all comparable to those obtained for patients with pure depressions. The rate of remission for patients with involutional melancholia was 86.9 per cent, and for those with the paranoid type of involutional psychosis it was only 43.7 per cent. The difference is even more striking when the number of treatments is considered. Patients with involutional depressions usually received 8 treatments; patients with the paranoid type were given at least 20 treatments as routine. The outcome of the illness in the paranoid patients, like that in the schizophrenic patients, was largely dependent on the duration of the disease.

Schizophrenia.—Proper emphasis must be placed on the necessity for an adequate number of convulsions in the treatment of schizophrenia. Cerletti,[4] in accordance with his experience in pharmacologic convulsive therapy, stated that 15 to 40 convulsions were required in the treatment of dementia praecox. The frequently reported failure of electric convulsive therapy for patients with schizophrenia is largely explained by the disregard of this requirement by the originator of the method, who stated with reference to insulin and convulsive treatment: "In the discovery of the new therapies the salient point is not the type of treatment applied but the courage of the therapeutist in repeating the application again and again." There is agreement on the necessity of production of a long series of comas in insulin therapy; the same need holds good for electric convulsive treatment. Here, unfortunately, the temptation toward abbreviation of the treatment is greater because most schizophrenic patients with a reasonable chance of improvement become temporarily free from symptoms after 4 applications. This customary early response to convulsive therapy influences the relatives, as well as the physician, to discontinue the treatment. Such a procedure accounts for the frequent statement that schizophrenic persons treated by means of convulsions usually relapse. Study of the literature on metrazol treatment reveals that results comparable to those in favorable reports on insulin therapy were obtained only by workers who gave 20 to 30 treatments, even in those cases in which early improvement was attained.[5] The same is true for the few reports on larger series of schizophenic patients who were given electric shock.[6] My experience has confirmed fully the necessity for long treatment of schizophrenia. Treatment of a group of 20 patients with acute schizophrenia was tentatively discontinued when they were free of symptoms after 10 applications; most of them had a relapse. After treatment was resumed, a satisfactory number of them were discharged with full remission of the disease.

4. Cerletti, U.: L'elettroshock, Riv. sper. di freniat. 64:209, 1940.

5. Zeifert, M.: Results Obtained from the Administration of 12,000 Doses of Metrazol to Mental Patients, Psychiatric Quart. 15:772, 1941.

6. Neymann, C. A.; Urse, V. G., and Madden, J.: Electric Shock in the Treatment of Schizophrenia and Other Mental Disorders, J. Nerv. & Ment. Dis., to be published. Kalinowsky, L., and Worthing, H. J.: Results with Electric Convulsive Treatment in Two Hundred Cases of Schizophrenia, Psychiatric Quart. 17:144, 1943. Reznikoff, L.: Comparison of Metrazol Convulsive Therapy with Electric Shock in Treatment of Schizophrenia, Arch. Neurol. & Psychiat. 49:587 (April) 1943.

Gratifying results were obtained from a long course of treatments in patients with acute schizophrenia (table 2). The rate of remission ("recovered and much improved") was 68.3 per cent for patients ill less than six months, 41.5 per cent for patients ill from six months to two years and only 9.2 per cent for patients ill more than two years. Thus, the rate of remission was satisfactory when the disease was of short duration but decreased rapidly when the psychosis was of longer standing. Patients with a history of previous attacks and remissions have a rather favorable prognosis for the new attack. Of 46 such patients, 26 (56.5 per cent) had a subsequent remission after treatment.

The patients who were judged by the staff of the institution as "recovered" or "much improved" were listed together because the term "recovered" was avoided as much as possible. Lewis[7] pointed out that a strictly scientific evaluation of results will be possible only when criteria for the various degrees of improvement are established. The practical question whether or not the method is of value in the treatment of schizophrenia can be answered in the affirmative in view of the figures presented; i. e., figures for remissions in patients ill less than six months were approximately twice as high as most figures reported for spontaneous remissions.[8] All the patients indicated in the tables under the heading "Recovered and Much Improved" left the hospital; in addition, approximately one third of the patients whose condition was "improved" left the hospital. The high rate of parole is a rather reliable expression of the effectiveness of therapeutic methods in institutional practice, where the release of the patient represents a legal responsibility.

It may be mentioned that patients with catatonic excitement and paranoid schizophrenia showed the best response. The illness of patients with catatonic stupor had a less satisfactory final outcome, although the motor symptoms could easily be broken up. Young patients with hebephrenia had the poorest treatment prognosis. It will be noted that the response of the various subtypes of schizophrenia to electric convulsive therapy is similar to their response to insulin.

The rate of relapse is low if a course of at least 20 treatments is given. Early relapses nearly always occurred during the first two weeks after treatment; they are indicated in table 2 under the heading of "Unimproved" because no patient was classified before his release from the hospital, or only three weeks after treatment. A recent follow-up study of 111 patients paroled from the hospital six months to two years ago revealed that only 13 had been returned to the hospital, several of whom were again treated and paroled. A follow-up study of these patients for several years is under way.

The most favorable prognostic factor is a short duration of the illness. Therefore early treatment of schizophrenia is imperative. The second important prognostic factor is the type of onset: The great majority of those patients whose illness had a favorable outcome had a history of acute onset; in most patients representing therapeutic failure the disease developed insidiously. This probably accounts for the better results for the institutional group and the less favorable results for the patients undergoing voluntary treatment at the Psychiatric Institute.[8a] Patients who come voluntarily to a psychiatric hospital usually have had a less acute development of the psychosis, and therefore are treated later, than those with acute

7. Lewis, N. D. C.: The Present Status of Shock Therapy of Mental Disorders, Bull. New York Acad. Med. **19**:227, 1943.

8. Guttmann, E.; Mayer-Gross, W., and Slater, E. T. O.: Short Distance Prognosis of Schizophrenia, J. Neurol. & Psychiat. **2**:25, 1939.

8a. Pacella, B. L., and Barrera, S. E.: Follow-Up Study of a Series of Patients Treated by Electrically Induced Convulsions and by Metrazol Convulsions, Am. J. Psychiat. **99**:513, 1943.

symptoms, who early come into conflict with society and have to be committed to an institution. Psychoneurotic symptoms, which also are more frequent among schizophrenic patients who are voluntarily admitted and patients with borderline conditions, carry an unfavorable prognosis. This is especially interesting in view of the failure of electric convulsive therapy of the pure neuroses. Such differences in material, made available through the opportunity to carry on treatments simultaneously at two hospitals representing different types of material, permit conclusions with regard to discrepancies: In contrast, conclusions reached through the adding of figures from several hospitals with dissimilar material are inconclusive. Another reason for discrepancies in the various reports is the aforementioned difference in procedure and number of treatments, which in a recent compilation of statistics on electric convulsive therapy led to a wide variation in figures, even among hospitals with probably similar material.[9] Comparisons can be made only when a similar technical procedure is applied to homogeneous material. The average number of applications indicated in some statistical reports is meaningless because they usually include high values for patients with hopeless, chronic illness who received a long course of treatments, so that the average number of applications for the whole series was raised. On the other hand, treatment of patients with a good response, who should have had a long course of therapy, was discontinued after a few sessions, when they were temporarily free of symptoms, and these patients generally had a relapse. These points are stressed because the work on shock therapy has been discredited by incompatible discrepancies, although the reasons for them are rarely examined.

Electric convulsive therapy of schizophrenia leads to satisfactory results only when it is applied systematically. This can be accomplished only when the cooperation of the relatives is secured. They should be informed of the necessity of a long course of treatments even in case of an immediate improvement. Although they may be pleased with this first symptomatic improvement, they must be warned of the probability of a confusional state toward the end of the course so that this otherwise unexpected development will not be taken as a turn for the worse and lead them to object to continuation of the treatment. After 20 convulsions the patient must be kept under observation for at least three weeks. An unsatisfactory result is usually apparent within two weeks, when the confusion clears up and residual symptoms become recognizable; in this event, 10 more treatments are given. If no definite improvement is noticeable at any time during the period of the first 20 convulsions, further treatment will not change the situation, and the course should be discontinued. Prolonged application of electric convulsive therapy is useless for patients who do not give an early response, but it is imperative for patients who have shown the possibility of a remission by favorable initial improvement.

Symptomatic Treatment.—It should be mentioned that the simplicity of the technic and the change of behavior after as few as 3 or 4 treatments make a short course of electric convulsions suitable for brief, purely symptomatic treatment of patients with a chronic psychosis for whom no final remission can be expected. A maintenance treatment with weekly, biweekly or even monthly applications, possibly 2 on the same day, will keep such patients on a higher level and facilitate their management. The importance of this measure in times of shortage of personnel is obvious. It may also help in keeping patients who have shown insufficient improvement outside the hospital. In military psychiatry, such symp-

9. Malzberg, B.: The Outcome of Electric Shock Therapy in the New York Civil State Hospitals, Psychiatric Quart. **17**:154, 1943.

tomatic treatment may be of aid in facilitating the removal of men with acute psychoses from distant theaters of war.

Psychoneuroses.—For these disorders the usefulness of electric convulsive therapy is not yet established. In 50 psychoneurotic patients [10] who were treated at the New York State Psychiatric Institute favorable responses occasionally occurred, but they were too rare to warrant recommendation of electric shock for the neuroses, except psychoneurotic depressions. In some instances of chronic, severe obsessive-compulsive neuroses in which psychotherapeutic methods have failed, an attempt may be justified. Obsessive thoughts or compulsions may disappear or become less troublesome during the confusional state of a long course of electric convulsive treatments, but they usually return shortly. The patient's increased accessibility can be used to advantage for a better psychotherapeutic approach,[11] but it should not be looked on as an actual remission. Occasional helpfulness of the electric convulsive treatment of the neuroses as an adjunct to psychotherapy cannot be considered comparable in type or degree to improvement which can be achieved with certain forms of psychoses. Psychotherapy continues to be the treatment of choice for most psychoneuroses.

COMPLICATIONS, SIDE EFFECTS AND CONTRAINDICATIONS

Serious complications in electric convulsive therapy are rare. This is not surprising since they hardly ever occur during the spontaneous convulsions of epileptic patients. In my material of more than 1,500 patients no fatality has occurred.

Cardiovascular distress of short duration was seen twice during nonconvulsive responses, but never during convulsions. Respiratory arrest appears to be the only danger in electric convulsive therapy. It was noted that such a complication is not remedied by attempts at chemical stimulation of the respiratory center but that artificial respiration is the only effective procedure. Since one experience of an alarming incident [12] of long respiratory arrest, a few artificial respiratory movements have been induced routinely in all patients showing even the slightest delay in respiration.

Fractures of the vertebrae have received undue attention. They represent more or less indistinct roentgenographic changes, of little clinical importance, and can be largely prevented by appropriate hyperextension of the patient during the convulsion.[13] Of far greater clinical importance, although rare, are fractures of other bones, such as the head of the femur or humerus, the scapula and the acetabulum. In the material of this report 3 instances of fracture (of the humerus, femur and acetabulum respectively) occurred when especially tight manual restraint was employed. Since these occurrences, tight restraint has been strictly avoided, and only light protection of the arms is applied, in order to protect the patient against possible dislocation of the shoulder, such as occurs in spontaneous epileptic attacks, but no attempt is made to prevent fractures by fixation of the head either of the femur or of the humerus in its articular cavity. As a consequence of this change in technic, no more fractures have occurred in the course of several thousand convulsions. The rarity of fractures and their apparent preventability do not seem to warrant the

10. Kalinowsky, L.; Barrera, S. E., and Horwitz, W. A.: The Question of the Usefulness of Electric Convulsive Therapy in the Psychoneuroses, to be published.

11. Selinsky, H.: Selective Use of Electro-Shock Therapy as an Adjuvant to Psychotherapy, Bull. New York Acad. Med. **19**:245, 1943.

12. Brill, H., and Kalinowsky, L.: Asphyxial Episodes and Their Prevention in Electric and Other Convulsive Therapies, Psychiatric Quart. **16**:351, 1942.

13. Worthing, H. J., and Kalinowsky, L.: The Question of Vertebral Fractures in Convulsive Therapy and in Epilepsy, Am. J. Psychiat. **98**:533, 1941.

routine use of curare and other drugs [14] which diminish muscular contraction, but which otherwise complicate the treatment, increase the patient's apprehension and do not seem to be without danger.

The most unpleasant side effect of electric convulsive therapy is impairment of memory. Some patients, especially psychoneurotic subjects, complain of their disturbance of memory, whereas others remain unaware of it. Closer study of this defect by several workers [15] has shown that the actual impairment is less pronounced than is indicated clinically. No permanent defect remains, even in cases of severe confusional states. It is important to differentiate this organic syndrome, which should not be considered as a sign of a reactivated psychosis; even when severe, it disappears within one or two weeks, so that it is not a deterrent to a long course of treatments when such is indicated. On the other hand, misinterpretation of organic mental symptoms sometimes leads to unnecessary continuation of treatment because these symptoms erroneously are taken as residual expressions of the original psychosis, rather than as transient effects of treatment.

Electroencephalographic changes [16] are usually reversible and should not be regarded as an indication for interruption of treatment. Discussion of pathologic changes in the brain is beyond the limits of this paper, but it may be mentioned that a report of hemorrhages [17] has not been confirmed by recent studies.[18] There seems to be no danger of the development of a convulsive state after electric convulsive treatment; only 1 patient, with a pretreatment convulsive pattern in his electroencephalographic record, had post-treatment seizures—in his case two seizures several months after treatment. On the other hand, 2 schizophrenic patients with traumatic epilepsy had an unusually long period without spontaneous convulsions after a course of more than 20 electric convulsive treatments.[19]

Contraindications to treatment are disease of the coronary arteries and serious cerebral lesions. In cases of most other concurrent diseases the severity of the physical condition and that of the psychosis have to be carefully weighed. For instance, in cases of agitated depression, myocardial damage and arterial hypertension have not been considered contraindications to treatment of the mental condition. On the contrary, successful therapy in several such cases led to the concept that immediate treatment is imperative when the psychotic excitement causes constant strain on an already damaged heart. The same consideration holds good in certain cases of tuberculosis in which psychotic exhaustion or feeding difficulties may represent an important indication for treatment. The favorable outcome in such cases may be understood by absence of the action of any drug in electric

14. Cash, P. T., and Hoekstra, C. S.: Preliminary Curarization in Electric Convulsive Therapy, Psychiatric Quart. **17**:20, 1943. Impastato, D. J.; Bak, R.; Frosch, J., and Wortis, S. B.: Modification of the Electrofit (Electroshock) by Various Drugs: I. Sodium Amytal, paper read at the Ninety-Ninth Annual Meeting of the American Psychiatric Association, Detroit, 1943.

15. Zubin, J., and Barrera, S. E.: Effect of Electric Convulsive Therapy on Memory, Proc. Soc. Exper. Biol. & Med. **48**:596, 1941. Sherman, J.; Mergener, J., and Levitin, D.: Effect of Convulsive Treatment on Memory, Am. J. Psychiat. **98**:401, 1941.

16. Pacella, B. L.; Barrera, S. E., and Kalinowsky, L.: Variations in Electroencephalogram Associated with Electric Shock Therapy of Patients with Mental Disorders, Arch. Neurol. & Psychiat. **47**:367 (March) 1942.

17. Alpers, B. J., and Hughes, J.: Changes in the Brain After Electrically Induced Convulsions in Cats, Arch. Neurol. & Psychiat. **47**:385 (March) 1942.

18. Barrera, S. E.; Lewis, N. D. C.; Pacella, B. L., and Kalinowsky, L.: Brain Changes Associated with Electrically Induced Seizures, Tr. Am. Neurol. A. **68**:31, 1942.

19. In a study published after this paper went to press it was shown that electrically produced convulsions increase the convulsive threshold and, therefore, may diminish spontaneous convulsions in epilepsy (Kalinowsky, L. B., and Kennedy, F.: Observations in Electric Shock Therapy Applied to Problems of Epilepsy, J. Nerv. & Ment. Dis. **98**:56, 1943).

convulsive therapy and by the fact that also in epileptic patients the seizures have surprisingly little bearing on the course of cardiovascular or other disease.

Although a large material has shown that complications, side effects and aggravations of preexisting physical conditions are less frequent than was anticipated, this observation should not lead to disregard of possible dangers and to the unwarranted use of electric convulsive therapy. However, when the treatment is strongly indicated, slight physical disorders should not discourage treatment of a severe mental condition.

SUMMARY

A review of electric convulsive therapy is presented on the basis of experience with 1,500 patients treated in two hospitals with different types of material. The importance of adequate treatment is emphasized, and several technical suggestions are given.

In the manic-depressive psychoses, manic states need more intense treatment than depressive states. Involutional psychosis of the paranoid type shows a less favorable response than does involutional depression.

Stress is placed on the efficacy of electric convulsive therapy in cases of acute schizophrenia when a sufficient number of convulsions is administered; discontinuation of treatment after the usually early clinical improvement leads almost invariably to relapse and is the most important reason for failure of this method in treatment of schizophrenia.

The results of electric convulsive therapy are less satisfactory for the psychoneuroses than for the psychoses.

No fatalities occurred in this material. Complications were rare and can largely be prevented.

Electroencephalographic changes and confusional states should not lead to discontinuation of treatment until an adequate number of convulsions have been given. Physical diseases may not be contraindications to therapy if they are aggravated by the mental condition.

722 West One Hundred and Sixty-Eighth Street.

MONILEMIA ASSOCIATED WITH TOXIC PURPURA

REPORT OF A CASE

ABRAHAM WIKLER, M.D.
Passed Assistant Surgeon (R), United States Public Health Service

EDWIN G. WILLIAMS, M.D.
Surgeon, United States Public Health Service
AND
CARL WIESEL, M.D.
Assistant Surgeon (R), United States Public Health Service
LEXINGTON, KY.

Several cases of infections of the blood stream with closely related strains of Monilia (e. g., Candida parakrusei), all occurring in drug addicts, have been found recently. A case of subacute endocarditis with systemic mycosis [1] and another case, almost identical except that there was cerebral involvement,[2] have been reported, with detailed autopsy observations. The organism in both cases was identified as C. (Monilia) parakrusei. In the present case, this organism was cultured from the blood stream of a patient, a drug addict, four days before his death. The clinical course and the autopsy observations were quite different from those in the 2 cases previously reported and may have been due to an unrelated, coincidental idiosyncrasy to a drug. Nevertheless, close study of the clinical record failed to rule out the possibility that the whole picture was one of invasion of the blood stream by C. (M.) parakrusei, and hence this case is reported.

REPORT OF CASE

History.—A white man aged 39, a physician, was first admitted to the United States Public Health Service Hospital, Lexington, Ky., on Nov. 22, 1940, for treatment of addiction to morphine. Examination disclosed nothing of note except chronic sinusitis and chronic otitis media on the left side. The urinalysis and blood count gave normal results, and the serologic reactions were negative. He made a good adjustment and was discharged as cured of the addiction after six months, his legal status being that of a probationer. On Dec. 13, 1941 he returned to this institution, disheveled, unkempt and reeking of paraldehyde. He stated that the court charged that he had been using drugs (morphine sulfate) for about five months and had advised him to return to the hospital for treatment. The patient denied these charges and stated that after he was discharged, in May 1941, he returned to his practice and soon became overworked. This, he stated, caused him to become "run down," and then he noted the appearance of "swellings" on the arms, forearms and thighs. He recalled that such "swellings" had appeared once before, several years ago, and were diagnosed as "rheumatic nodules"; they had persisted for a few weeks and then disappeared. Shortly after the lesions appeared the second time, there developed a condition which was diagnosed as pneumonia, and sulfathiazole was administered orally. The patient stated that he had been hospitalized until a few days before his readmission to this hospital, and that just before he left home to come to this institution he was given 2 ounces (62 Gm.) of paraldehyde and a half-grain of

From the United States Public Health Service Hospital, Lexington, Ky.

1. Joachim, H., and Polayes, S. H.: Subacute Endocarditis with Systemic Mycosis (Monilia), J. A. M. A. **115**:205-209 (July 20) 1940. Polayes, S. H., and Emmons, C. W.: Final Report on Identification of the Organism of Previously Reported Case of Subacute Endocarditis and Systemic Mycosis (Monilia), ibid. **117**:1533-1534 (Nov. 1) 1941.

2. Wikler, A.; Williams, E. G.; Douglass, E. D.; Emmons, C. W., and Dunn, R. C.: Mycotic Endocarditis: Report of a Case, J. A. M. A. **119**:333-336 (May 23) 1942.

morphine sulfate (0.032 Gm.) by a physician. He was unable or unwilling to account for his unkempt appearance. He denied emphatically that the "swellings" on the extremities were due to unsuccessful attempts at intravenous injections (self administered) of drugs, such as pentobarbital (a practice which is rather common among drug addicts).

Examination.—On admission the patient was drowsy, and speech was slurred; but on his being persistently questioned, he was able to give a more or less coherent history, and he was well oriented. Gait was extremely ataxic, and he could not walk without support. The pupils were miotic. The heart and lungs were normal. The blood pressure was 120 systolic and 80 diastolic. Examination of the abdomen, genitalia and rectum revealed nothing abnormal. Numerous subcutaneous tumors were visible and palpable over the inner aspects of the thighs, the lateral aspects of the arms and the dorsa of the forearms. Some were firm; others were fluctuant, but none was draining. They varied from the size of a marble to that of a small egg. The overlying skin was not erythematous and in some places was freely movable over the tumor; in other places the tumors appeared to be attached to the skin. One of these masses, on the inner aspect of the left thigh, had been incised, but the wound had healed. There was considerable swelling about a mass just superior to the left patella, and the patient kept the left knee flexed, complaining of pain when it was moved. The oral temperature was 37 C. (98.6 F.), the pulse rate 84 and the respiratory rate 19 per minute.

Laboratory Data.—Urinalysis revealed a specific gravity of 1.021, a p_H of 4.5 and absence of albumin or sugar; microscopic examination showed nothing significant. The blood count showed 85 per cent hemoglobin, 4,270,000 red blood cells and 8,200 white blood cells, of which 79 per cent were polymorphonuclear leukocytes (including 5 per cent band cells), 16 per cent lymphocytes, 2 per cent eosinophils and 3 per cent large mononuclears. The serologic reaction of the blood was negative.

Course of Illness.—In spite of the absence of significant laboratory evidence, the patient appeared to be ill. He was generally drowsy but complained of aching of the extremities, especially the left knee. At no time did he show any of the objective signs of an opiate abstinence syndrome. Complete neurologic examination on the morning after admission revealed no abnormality except drowsiness. He again denied that he had injected any drug into his skin. Material from one of the nodules was aspirated, and a smear revealed numerous pus cells, many red blood cells but no organisms. However, the possibility that these nodules were simple staphylococcic abscesses could not be ruled out, and sulfathiazole, 1 Gm., was administered orally every four hours. In addition, a proprietary preparation of organic tin and protein in tablet form, each tablet containing 22 mg. of metallic tin, was prescribed, 1 tablet to be given four times daily. He also received phenobarbital, 3 grains (0.18 Gm.), in the morning, pentobarbital sodium, 3 grains (0.18 Gm.), in the evening and codeine sulfate, 1 grain (0.065 Gm.), four times daily for relief from pain, with administration of nicotinic acid, thiamine hydrochloride and infusions of 5 per cent dextrose in a solution of sodium chloride as supportive measures. However, sulfathiazole caused vomiting, and the drug was discontinued after twenty-four hours. The other medication was continued as before. The subcutaneous nodules began to grow smaller, and his condition appeared to be stationary, although at no time could it be said that his sensorium was entirely clear.

On December 21 it was noted that the patient appeared more listless and drowsy than heretofore. The next day neurologic examinations revealed stupor, periodic breathing, a bilateral Babinski sign and apparent flaccidity of the left upper extremity. Urinalysis (catheterized specimen) revealed a specific gravity of 1.012, a 2 plus reaction for albumin, absence of sugar, an occasional white blood cell and a few red blood cells. The blood count showed 70 per cent hemoglobin, 3,650,000 red blood cells and 14,100 white blood cells, of which 76 per cent were polymorphonuclear leukocytes, 22 per cent small mononuclears, 1 per cent large mononuclears and 1 per cent eosinophils. The coagulation time was two minutes and the bleeding time five minutes. The nonprotein nitrogen content of the whole blood was 75 mg. and the sugar content 67.5 mg. per hundred cubic centimeters. Lumbar puncture revealed that the cerebrospinal fluid was clear and under an initial pressure of 360 mm. of water (with the patient recumbent on his left side). After withdrawal of about 25 cc. of fluid, the pressure fell to 165 mm. of water. Analysis of the cerebrospinal fluid revealed a cell count of 2 per cubic millimeter, 0.36 Gm. of protein per liter, 51.3 mg. of sugar and 647 mg. of chlorides per hundred cubic centimeters, a negative Kolmer reaction and a colloidal gold curve of 0000000000.

Roentgenograms of the chest, taken at the bedside, were reported as follows: "Examination on December 22 showed a minimal amount of scattered bronchial infiltration in both lungs. The next day slight pleural thickening appeared on the right side, with perhaps some pleural

fluid. Radiating from each hilar region were densities which had the appearance of 'uremic butterfly.' However, the same appearance might result from congestive changes."

Treatment consisted of intravenous injections of 50 per cent dextrose and administration of digitalis and respiratory stimulants. The patient, however, became more stuporous; coarse rales appeared in the bases of both lungs, and pronounced oliguria supervened.

On December 23 examination of a catherized specimen of urine showed a specific gravity of 1.014, a 2 plus reaction for albumin, absence of sugar, many red blood cells, a few granular casts and a few epithelial cells. The nonprotein nitrogen content of the whole blood was 88.2 mg. per hundred cubic centimeters. The hemoglobin measured 50 per cent; the red blood cells numbered 1,980,000 and the white blood cells 16,100, of which 84 per cent were polymorphonuclear leukocytes, 15 per cent small mononuclears, and 1 per cent large mononuclears.

Fig. 1.—Coronal section through cerebrum and pons, showing diffusely scattered petechial hemorrhages.

A blood transfusion was performed, but the patient's condition became rapidly worse; he showed signs of pulmonary edema and died on December 25, twelve days after admission. Blood had been taken for culture on December 21, but up to the time of the patient's death no growth was seen. Ten days later the same specimen revealed a pure growth of a yeast-like organism similar in all respects to C. parakrusei.

Clinical Diagnosis.—The diagnosis under consideration, before autopsy was performed and before culture of the blood yielded any growth, were (1) periarteritis nodosa, with involvement of the brain, heart and kidneys, and (2) acute nephritis, with death due to uremia.

Necropsy.—Essential changes: There were some subcutaneous nodules in the arms and legs. Histologic examination of two nodules removed from the subcutaneous tissue on the lateral aspect of the right arm revealed focal accumulations of numerous multinucleate giant cells associated with an infiltration of lymphocytes and plasma cells and proliferation of fibroblasts. A moderate amount of foreign body material was present in many of the giant cells. One of the granulomatous foci revealed tissue necrosis. There were also areas of focal

congestion, edema, hemorrhage, deposition of fibrin, thrombosis of small vessels and infiltration with small to moderate numbers of polymorphonuclear leukocytes and lymphocytes.

When the body was opened, both lungs were observed to be slightly adherent to the wall of the chest. The right pleural cavity contained considerable straw-colored fluid. Both lungs were mottled and of irregular consistency on palpation. Cross section revealed the typical blotchy appearance of terminal lobular pneumonia. Frothy, blood-tinged fluid could be scraped from the cut surface. Histologically the lungs showed rather extensive lobular pneumonia, with zones of necrosis in the central areas. The blood vessels in the lungs showed practically no changes. There were, however, focal hemorrhages and edema.

Inspection of the heart showed practically complete obliterative pericarditis; otherwise the gross appearance of the heart was not remarkable. Histologically there was slight focal interstitial fibrosis of the myocardium. The epicardial fat showed congestion, extravasation of blood and irregular infiltration with polymorphonuclears, lymphocytes and macrophages.
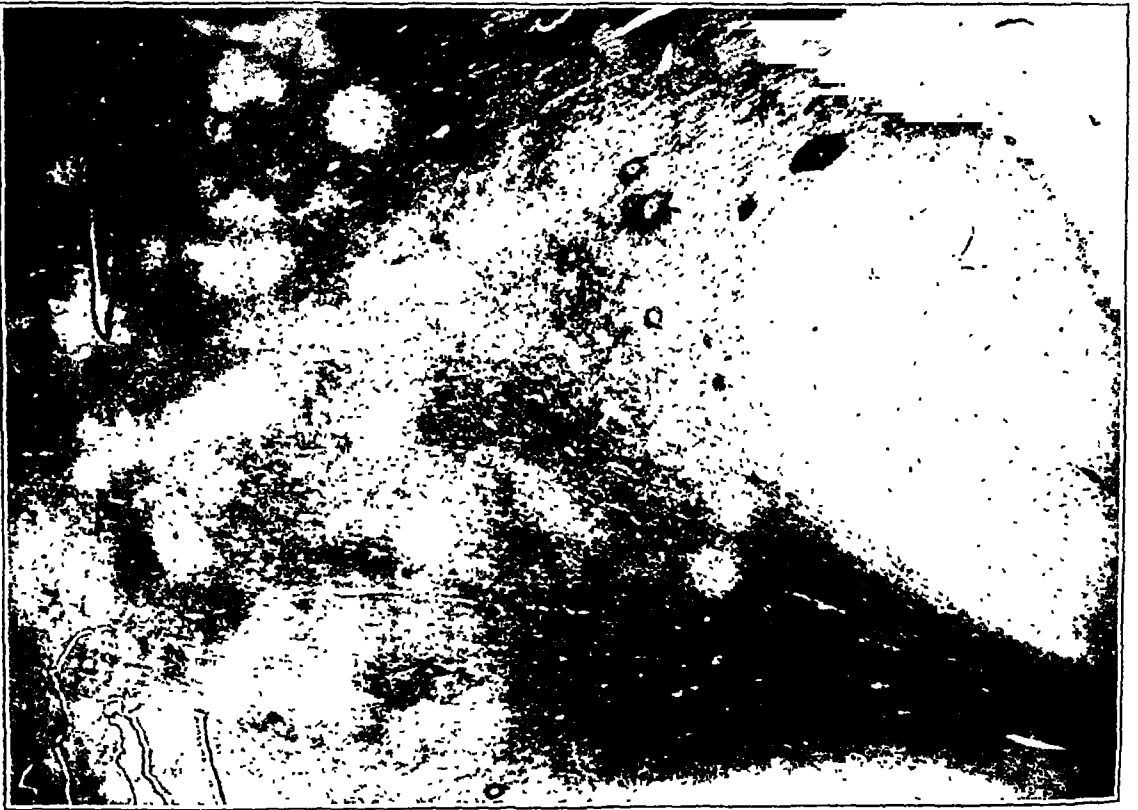
Fig. 2.—Section from the right parietal region, showing irregular patches of demyelination. Spielmeyer method for myelin sheaths.

There were a number of small, hard nodules and a few hemorrhagic areas in the pancreas. Histologically there were some interlobular and interacinar edema and local extravasation of blood.

The adrenals were not grossly abnormal. Histologic study of adipose tissue around the adrenals, however, showed areas of edema, with deposition of fibrin and some extravasation of blood accompanied by infiltration of macrophages.

The liver presented a nutmeg appearance externally and on cross section. Histologically there were extensive central necrosis and passive congestion. Peripheral to the congested zones there was evidence of hypertrophy of the liver cells with vacuolization.

A section of mesentery showed retroperitoneal purpura.

The spleen presented evidence of passive congestion, and histologic examination revealed passive congestion, with considerable depletion of the lymphoid tissue. There was some reticuloendothelial hyperplasia.

The kidneys showed no gross pathologic change, although there had been anuria and a high nonprotein nitrogen content of the blood for some time before death. Histologic study

revealed considerable degeneration of the epithelial lining of the convoluted tubules, many of which contained granular material. There were some interstitial fibrosis and some edema. The arterioles and larger arteries showed no abnormalities. There was moderate separation of cortical tubules in irregular areas by loose fibrillar and collagenous tissue, which was infiltrated with small to moderate numbers of lymphocytes and plasma cells and fewer polymorphonuclear leukocytes.

The stomach was opened and the mucosa examined. There was nothing unusual about the stomach, in spite of the fact that the patient had vomited blood.

Brain: The brain showed pronounced injection of the leptomeninges, especially in the right occipitoparietal region. The subarachnoid space was distended with clear fluid. The cerebral hemispheres were symmetric and firm. The vessels at the base of the brain were patent. Hemorrhagic petechiae (fig. 1), varying in size from a pinpoint to a pinhead, were scattered diffusely throughout the brain, including the hemispheres, the brain stem and the
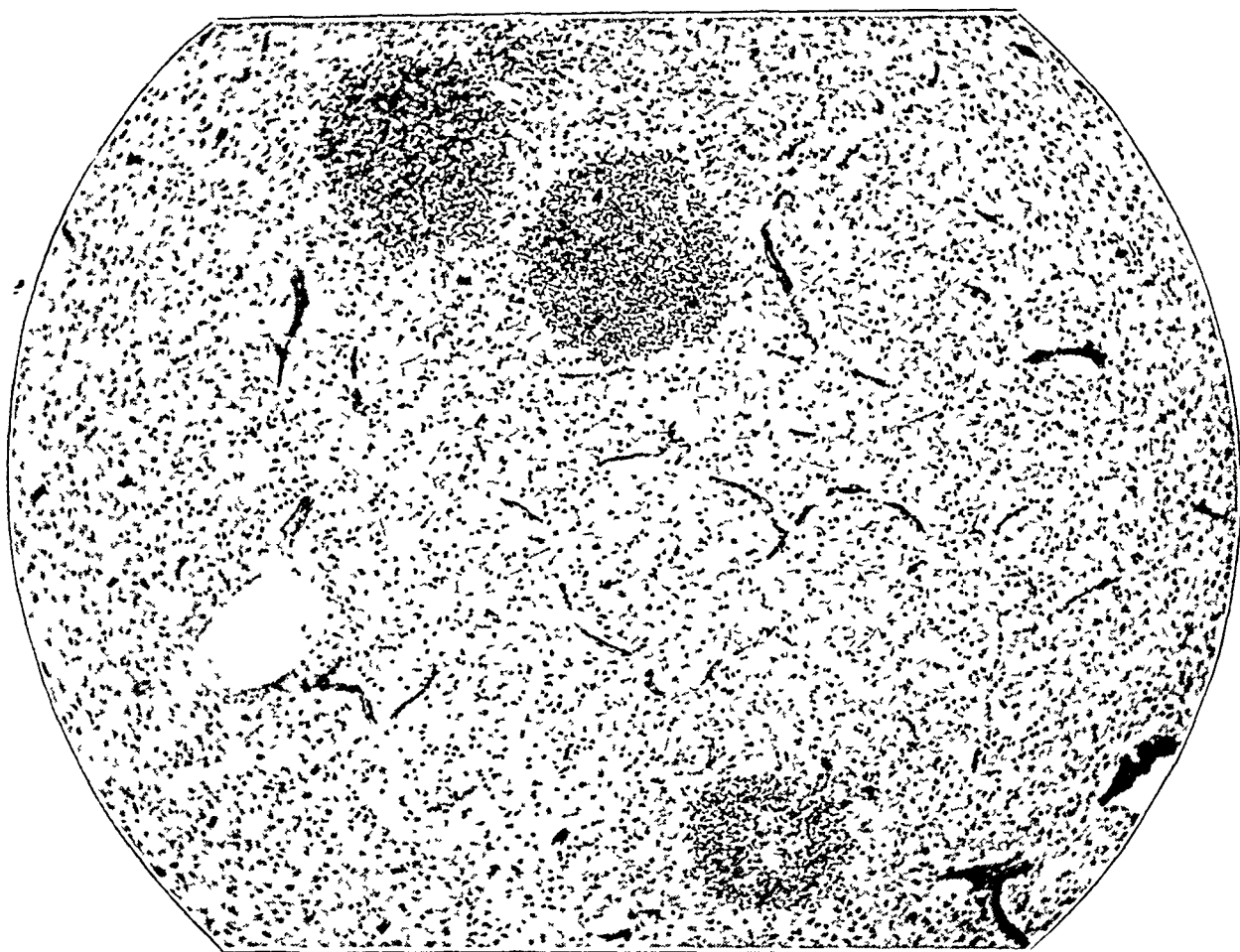
Fig. 3.—Section from the same block as that from which was taken the section in figure 2, showing pericapillary hemorrhages and absence of glial proliferation.

cerebellum. The white matter was involved to a much greater extent than the gray matter. These lesions were not concentrated in any particular region of the brain, but larger focal hemorrhages were observed in the right cerebellar hemisphere. The ventricular system was patent throughout.

Histologically, the brain showed hemorrhages surrounding many of the capillaries. There was no lymphoid cuffing, and at no place was there evidence of inflammation. In many of these hemorrhages there were central zones of necrosis, around which were grouped glia cells. The histopathologic comment was as follows: "The purpura may be secondary to infection with C. parakrusei, but this cannot be confirmed, since careful search failed to reveal any organisms in the lesions."

Further microscopic study of the cerebral lesions showed that these were due to an acute toxic process and were not embolic or infectious. Diffusely scattered, irregular, patchy areas of demyelination, bearing no constant relation to the pericapillary hemorrhages, were revealed by the Spielmeyer method for staining of myelin sheaths (fig. 2). No glial proliferation was seen in sections stained by the silver carbonate method of Rio Hortega (fig. 3) or by the

gold chloride–mercury bichloride method of Ramón y Cajal. However, in sections stained by the latter method, evidence of an acute destructive process was indicated by fragmentation and distortion of many astrocytes in the vicinity of the lesions (fig. 4). No abnormal accumulation of fat was seen in fat ponceau preparations.

Postmortem Diagnoses.—The diagnoses were (1) secondary purpura, involving the brain, lungs, kidneys, pericardium and retroperitoneal and subcutaneous tissues; (2) focal foreign body reaction in subcutaneous tissues; (3) reticuloendothelial hyperplasia in the spleen; (4) parenchymatous degeneration of the kidneys; (5) acute bronchitis and bronchopneumonia (pleuritis with effusion); (6) chronic passive congestion of the viscera, with fatty metamorphosis in the liver; (7) adhesive pericarditis, and (8) interstitial myocardial fibrosis.

Bacteriologic Report.—A specimen of the growth obtained from culture of the blood was studied by Dr. C. W. Emmons, senior mycologist, National Institute of Health, Bethesda, Md., who reported that the organism appeared to be a typical strain of C. parakrusei, corresponding in all respects to the strain previously reported on.[2]
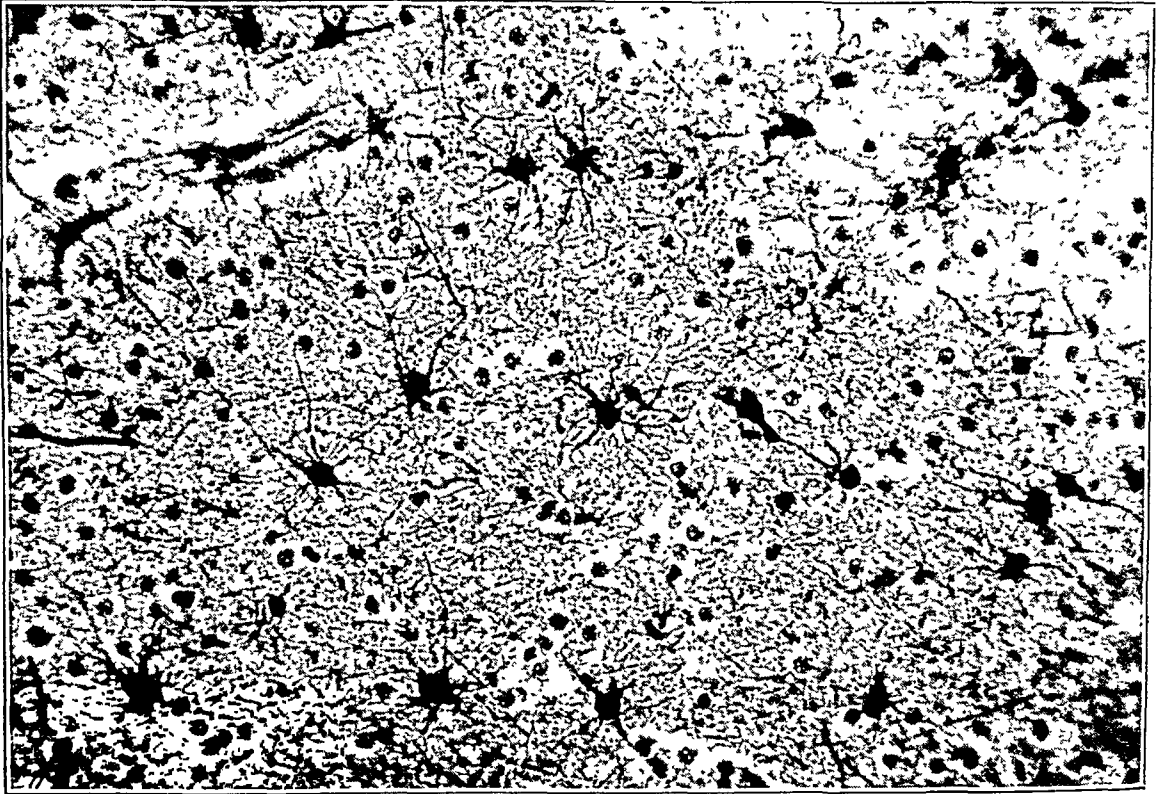
Fig. 4.—Section from the same block as that from which was taken the section in figure 2, showing fragmentation and distortion of some astrocytes in the vicinity of the lesion (at the right), while astrocytes farther away are well preserved.

COMMENT

The observation of C. parakrusei in the patient's blood stream was a complete surprise to us. The possibility of contamination appears to be definitely ruled out, since the only other time that this organism has been isolated in this laboratory was in November 1940, in a case of mycotic (C. parakrusei) endocarditis.[2] As to the source of the infection, we can only speculate, but it appears most likely that the organism was introduced into the body together with some drug at the sites of the subcutaneous nodules. It is evident that the patient gave a false history on admission, possibly to avoid legal complications. The presence of crystals and foreign body reactions in these nodules proved that the patient had injected a rather irritating substance locally and that this substance was not pure morphine

sulfate, but probably a "bootleg" narcotic. (It is unlikely that the substance was pentobarbital, since the latter causes rather typical round, punched-out ulcers of the skin.)

As to the cause of the severe anemia and the purpuric lesions in the brain, heart, lungs and kidneys, analysis of the clinical course and autopsy observations leads us to the following considerations: Obviously, except for the terminal pneumonic lesions, there was no true infection, so that acute nephritis and periarteritis nodosa are eliminated. The acute hemorrhagic encephalitis of Strümpell is also eliminated because this condition usually occurs in younger persons and definite pathologic evidence of inflammatory reactions are seen. The lesions appear to have been due, rather to some "toxic" agent.[3] We do not know the nature of the drug the patient injected subcutaneously (certainly not an arsenical), but we do know that he was suffering from severe paraldehyde intoxication on admission. Death due to this condition is rare, but a few cases have been reported,[4] and the clinical course and the observations at necropsy were somewhat similar to those of the present case. Thus the cases of paraldehyde poisoning were characterized by rapid development of profound stupor and death due to pulmonary edema secondary to cardiac failure, while the pathologic changes were characterized by hemorrhagic lesions in the viscera and the results of cardiac failure. No report on the cerebral changes in death due to paraldehyde poisoning could be found in the literature, but it is known that "purpura cerebri" may result from severe anoxemia due to anesthesia.[5] However, in all cases of death due to paraldehyde poisoning reported in the literature, the patient died a day or two after ingestion of the drug, and symptoms of intoxication appeared within a few hours. In our case, except for persistent drowsiness, there were no alarming symptoms until eight days after the patient had taken the paralydehyde; the blood count and urinalysis revealed nothing abnormal until that time, and death occurred twelve days after his admission. Therefore, unless the case was one of an extraordinarily slow toxic effect of the drug, it is unlikely that paraldehyde poisoning was the cause of death.

A toxic reaction to sulfathiazole is unlikely because the patient, who received the drug for only twenty-four hours, vomited most of what he did take and did not show any change until four days afterward. Also, it is noted that the hemoglobin and the red blood cells were severely affected but the white blood cells were not affected, the reverse of the usual picture in cases of sulfathiazole intoxication. Codeine, phenobarbital and pentobarbital, in the doses given, could not have been responsible; at least no case of such a reaction has yet been reported. Allylisopropylacetylcarbamide (sedormid), which has often caused thrombopenic purpura,[6] was not administered in this case, and it is unlikely that the patient used it before admission, since no purpura or changes in the blood or urine were seen on admission. This leaves only the preparation of organic tin and protein as a possible toxic agent. However, no reports of a toxic reaction to this compound have been found. A case of severe anemia with renal involvement following ingestion of a compound of metallic tin and lead has been reported,[7] but Laporte

3. Freeman, W.: Neuropathology, Philadelphia, W. B. Saunders Company, 1933, p. 112.

4. Shoor, M.: Paraldehyde Poisoning, J. A. M. A. **117**:1534-1535 (Nov. 1) 1941. Kotz, J.; Roth, G. B., and Ryon, W. A.: Idiosyncrasy to Paraldehyde, J. A. M. A. **110**:2145-2148 (June 25) 1938.

5. Wilson, S. A. K.: Neurology, Baltimore, Williams & Wilkins Company, 1940, vol. 1, chap. 7, p. 84.

6. Falconer, E. H., and Schumacher, I. C.: Purpura Hemorrhagica Due to Ingestion of Sedormid (Allylisopropylacetylcarbamide), Arch. Int. Med. **65**:122-137 (Jan.) 1940.

7. Laporte, A.; Meyer, A., and Bousser, S.: Anémie grave aiguë, avec légère atteinte rénale, consécutive a l'absorption d'étain et de plomb métalliques, Bull. et mém. Soc. méd. de hôp. de Paris **55**:955-961 (June 26) 1939.

and associates expressed the opinion that the condition was due solely to lead poisoning.

We are left, then, with the distinct possibility that the patient's lesions were due to invasion of the blood stream by C. (M.) parakrusei or to a toxin produced by this organism. It should be noted that in the previous case [2] persistent anemia was exhibited, although the visceral and cerebral lesions were due to an embolic phenomenon rather than to purpuric lesions.

SUMMARY

A case of infection of the blood stream with C. (M.) parakrusei, with associated purpuric lesions in the brain, heart, lungs, kidneys and subcutaneous and retroperitoneal tissues together with anemia and uremia, is reported in detail. However, it is not possible to exclude with certainty the possibility that these changes were due to an extraordinarily slow-acting toxic effect of a self-administered overdose of paraldehyde.

ANEURYSM OF CIRCLE OF WILLIS ASSOCIATED WITH CONGENITAL POLYCYSTIC DISEASE OF THE KIDNEYS

FRANCIS M. FORSTER, M.D.

AND

BERNARD J. ALPERS, M.D.

PHILADELPHIA

Intracranial aneurysms are customarily divided into three chief etiologic types: congenital; arteriosclerotic and embolic. Of these three types, the congenital has proved the most interesting and in all probability the most numerous. The presence of defects in the media in this type of aneurysm was first shown by Forbus.[1] Richardson and Hyland[2] subsequently corroborated this observation.

Congenital anomalies are notoriously prone to occur in combinations, so that it is not surprising that congenital aneurysms have been reported in association with other developmental defects. The most frequently reported combination is that of aneurysm of the circle of Willis and coarctation of the aorta.[3] Congenital polycystic kidney also is associated with other anomalies, the most frequent developmental defects being aberrant biliary cysts of the liver and pancreatic cysts. Aneurysm of the cerebral arteries is sometimes found with congenital polycystic kidney, a combination which has been recorded previously.

The case which we record merits attention because of the rare combination of cerebral aneurysm and congenital polycystic kidneys and because the aneurysm occurred in a 13 week old infant. In view of the size and histologic characteristics of the aneurysm, the case is of value in shedding further light on the problem of congenital aneurysm.

REPORT OF A CASE

Advanced bilateral polycystic disease of the kidneys and small unruptured aneurysm of the circle of Willis.

History.—C. W. W., a boy aged 13 weeks, died en route to the Jefferson Medical College Hospital. He was born at the Coaldale State Hospital, the delivery being uneventful and without instrumentation. The weight at birth was 8 pounds 5 ounces (3,770 Gm.), and the child appeared normal on delivery. The parents noted nothing unusual after birth. The child continued to gain weight and at 10 weeks of age weighed 11 pounds 6 ounces (5,159 Gm.). When he was 7 weeks old he suffered an attack of loss of consciousness and pallor, the total duration of which was about fifteen minutes. After this his development was uneventful, until he was 11 weeks old, when a similar attack occurred. He was then admitted to the Coaldale

1. Forbus, W. D.: Origin of Miliary Aneurysms of Superficial Cerebral Arteries, Bull. Johns Hopkins Hosp. 47:239-284, 1930.

2. Richardson, J. C., and Hyland, H. H.: Intracranial Aneurysms, Medicine 20:1-84, 1941.

3. Parker, H. L.: Aneurysms of Cerebral Vessels: Clinical Manifestations and Pathology, Arch. Neurol. & Psychiat. 16:728-746 (Dec.) 1926. Weber, F. P.: Stenosis (Coarctation) of the Aortic Isthmus with Sudden Death from Rupture of a Cerebral Aneurysm, Proc. Roy. Soc. Med. 20:1227-1240, 1927. Woltman, H. W., and Shelden, W. D.: Neurologic Complications Associated with Stenosis of the Isthmus of the Aorta, Arch. Neurol. & Psychiat. 17:303-316 (March) 1927. Förster, A.: Sudden Death Due to Rupture of Aneurysm at Base of Brain in Aortic Stenosis, Deutsche Ztschr. f. d. ges. gerichtl. Med. 33:115-118, 1940. Koletsky, S.: Coarctation of Aorta Associated with Mycotic Aneurysm, Ohio State M. J. 38: 465, 1942.

State Hospital, where he had a consistent and unexplained fever, the temperature reaching as high as 104 F. On April 6, 1943 he was transferred to the Jefferson Hospital, but died before admission.

Necropsy.—Necropsy was performed by Dr. P. A. Herbut shortly after death. The anatomic diagnosis was congenital bilateral polycystic kidneys, marked cardiac hypertrophy of the left ventricle and partial pulmonary atelectasis.

The body was that of a fairly well developed, somewhat emaciated, white male infant approximately 2 months of age. The head was of normal size and shape, with patent fontanels. The eyes, ears, nose and mouth were normal. No tumor masses were seen in the neck. The chest was symmetric, and the abdomen was full. The external genitalia were those of a normal male infant. Over the posterior portion of the sacrum was a small depression in the skin, 2 mm. in diameter. An incision through this area failed to reveal any defects of the spinal canal.

All serosal surfaces of the thoracic cage were smooth and glistening. The heart weighed 40 Gm. It was about twice the normal size, the predominant enlargement being in the left
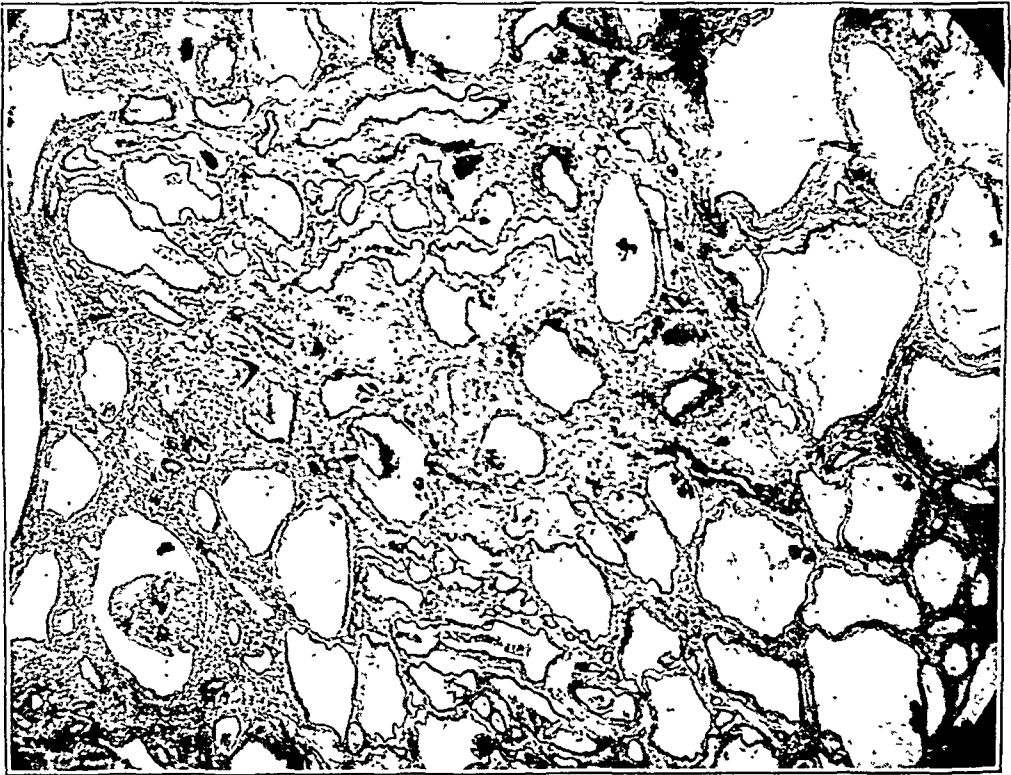
Fig. 1.—Section of kidney, showing severe polycystic disease. Hematoxylin and eosin stain; × 50.

ventricle. The myocardium was reddish brown and firm and was tremendously hypertrophied on the left side. The cardiac cavities showed no dilatation. No anomalies of the valves, cusps, leaflets or septum could be disclosed. The aorta was free of congenital anomalies. The left lung weighed 20 Gm. and the right 40 Gm. The posterior portions of both lungs contained small, irregular areas of partial atelectasis. The thymus was atrophied.

All serosal surfaces of the abdominal cavity were smooth and glistening. The spleen weighed 10 Gm. and showed no abnormalities. The liver was normal and weighed 250 Gm. The pancreas and adrenal glands were normal. The kidneys weighed 90 Gm. each and were tremendously enlarged. The renal capsules were adherent to such an extent that it was not possible to strip them. Immediately beneath the capsule and extending throughout the substance of the kidney were numerous small cysts, ranging from pinpoint in size to 4 mm. in diameter. These cysts were so numerous that virtually the entire substance of the kidney had been replaced by them. The demarcation between the cortex and the medulla was in large part obliterated. Sections of the kidneys (fig. 1) revealed almost no functioning malpighian corpuscles, the normal tissue having been replaced by numerous cysts.
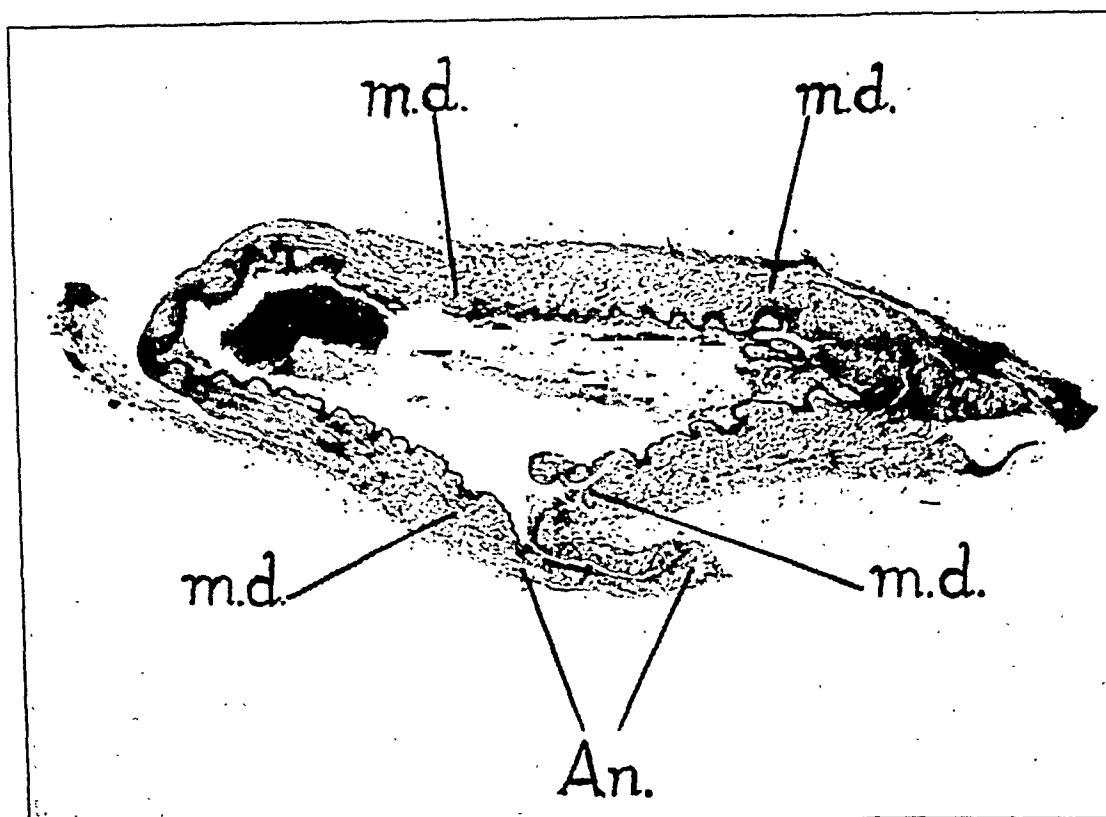
Fig. 2.—Section of the basilar artery before its bifurcation into the two posterior cerebral arteries. The aneurysm (*AN*) can be seen arising from the basilar artery, from an area where the media is absent. A similar area of defect in the media can be seen diametrically opposite the origin of the aneurysm. The edge of the medial defect is indicated by *m.d.*
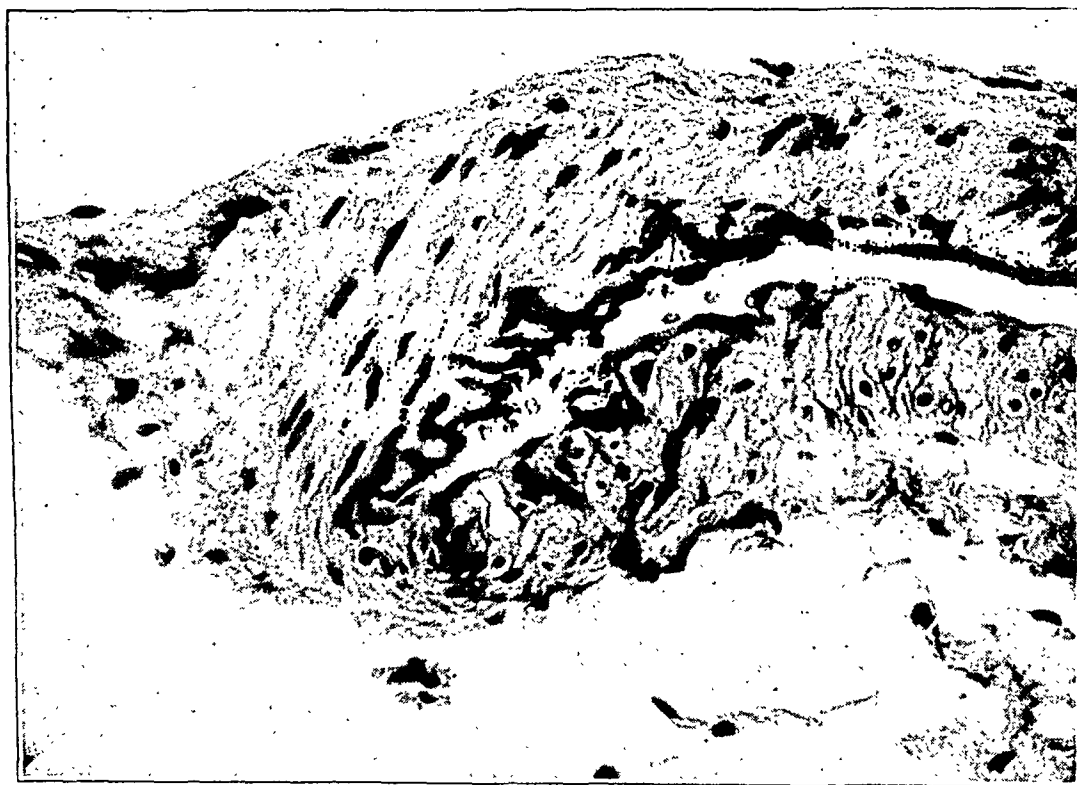
Fig. 3.—Wall of the aneurysm, demonstrating presence of the internal elastic membrane and absence of a well defined media. Hematoxylin and eosin stain; × 200.

Gross Description of the Brain.—The brain weighed 550 Gm. and measured 15 by 11 cm
The meninges, convolutions and gyri were normal. The circle of Willis was complete, and
no disproportion existed between the vessels. On the ventral surface of the basilar artery,
at the bifurcation into the two posterior cerebral arteries, was a small raised area, barely
visible macroscopically. This could not be removed by gentle friction. It measured about
1 mm. in diameter, appeared like a very small sac, was connected with the vessel wall and
had the appearance of a minute aneurysm. There were no other abnormalities of the vessels
comprising the circle of Willis. On coronal section the cerebrum, the cortical gray matter,
the centrum semiovale and the basal ganglia were normal. The ventricular system was of
normal size, shape and position except that the occipital horns of the lateral ventricles were
dilated moderately, symmetrically and uniformly. The periventricular white matter was
normal. The brain stem and the cerebellum were of normal size and shape and were sym-
metric Cross sections of these structures revealed no abnormality.
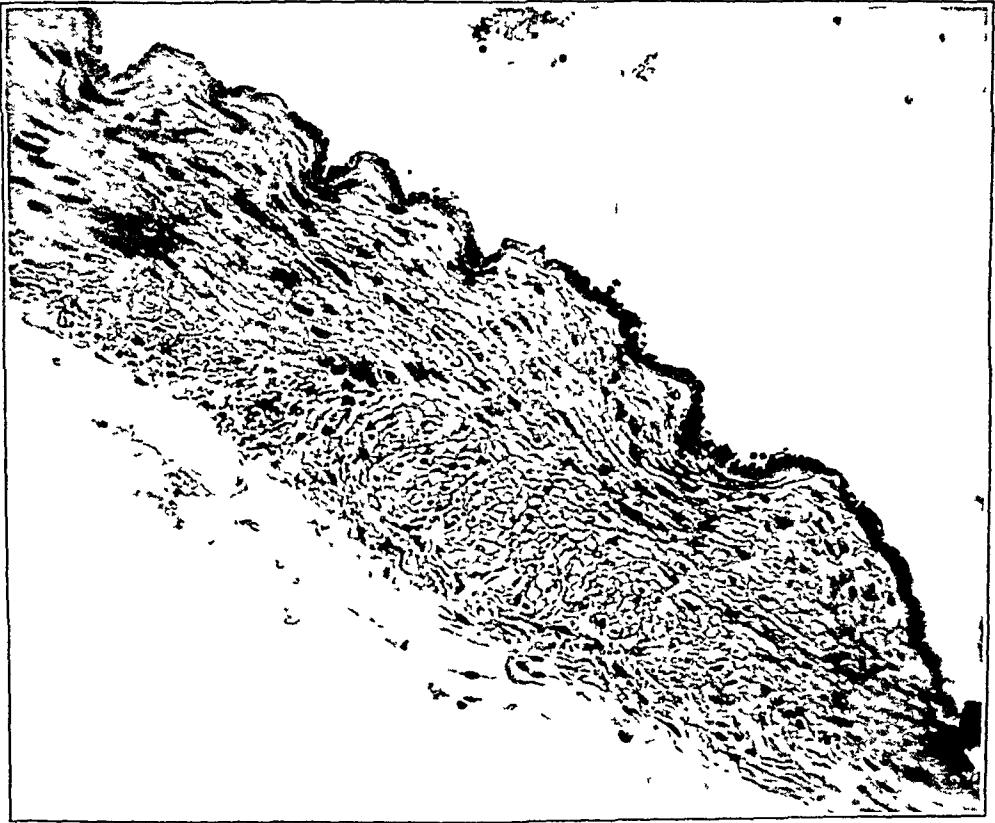
Fig. 4.—Wall of basilar artery, showing the defect in the media. Hematoxylin and eosin
stain; × 200.

Microscopic Description of Brain.—Serial paraffin sections were made of the basilar
artery, beginning well below the bifurcation and extending upward to the level of two
distinct posterior cerebral arteries. These sections included the entire expanse of the aneurysm.
In the most inferior sections two well defined and diametrically opposite defects of the
media were apparent in the wall of the basilar artery. When the sections were followed
superiorly, the aneurysm appeared as a small outpouching from one of these defective areas
in the media. The aneurysm presented a well defined internal elastic membrane, confluent
with that of the parent vessel. No evidence of a medial coat could be ascertained in any
of the sections through the aneurysm. The aneurysm, therefore, consisted of an intimal
lining, an internal elastic membrane and a rather loose adventitial tissue, containing occa-
sional smooth muscle fibers. Fresh red blood cells were present in some of the sections
through the aneurysm, and no thrombus was apparent. In the sections superior to the
origin the aneurysm was separated from the vessel, and eventually only the two posterior
cerebral arteries persisted. The aneurysm, therefore, consisted of an evagination from the
ventral wall of the basilar artery at the level of its bifurcation, was round and about 1 mm
in diameter and arose from an area of defect in the media.

Sections of the cortex revealed that the meninges were normal and the subarachnoid space was free of red blood cells. Partial narrowing of the lumens of the smaller vessels resulted from intimal thickening. This was best seen in the arterioles of the meninges. The cortex was immature, with poorly defined laminations. The ganglion cells were rounded, and the nuclei were frequently swollen. The pyramidal cells of layer V were seldom actually pyramidal. The nuclei of these cells were large, while the cytoplasm was reduced to a scant amount about the nucleus. The cell processes stained poorly and were frequently fragmented. Nissl substance was scant. There was little evidence of neuronophagia and no gitter cells. The cellular content and architectural arrangement of the white matter were normal. The ependymal lining, where present, consisted of a single layer of cells. Occasionally there were pockets of germinal epithelium, and beneath the ependyma was an area of increased cellularity, with immature ependymal cells predominating. These periventricular changes were more prominent about the posterior horns of the lateral ventricles. However, collections of immature ependymal cells, as pointed out by Alpers,[4] cannot be considered pathologic at this age.

COMMENT

The addition of this case to the literature is warranted because of the rarity of reported cases of polycystic kidney and congenital aneurysm and because of the value of the case in the elucidation of the problem of congenital aneurysm.

The earliest reported case of polycystic kidney and cerebral aneurysm was that of Dunger,[5] in 1904. This was followed by 5 reports, the total number of previous cases being thus brought up to 9. The table presents a summary of the previously reported cases. In all instances the patients were adults. In only 1 other case, that of Fearnsides,[6] was an unruptured aneurysm reported. In previous reports histologic studies of the aneurysms were not included. While in all previous cases the aneurysms occurred in the anterior portion of the circle of Willis, the point is of little note, since aneurysms are by far more common in this area than in the posterior portion.

It is quite likely that the association of aneurysm and polycystic kidney is much more frequent than the review of reported cases would indicate. Sieber[7] reported 212 cases of polycystic kidney, with 10 deaths due to cerebral hemorrhage. Coombs[8] noted 5 deaths from cerebral hemorrhage among 42 cases. Of 6 cases reported by Atonna and Morrissey,[9] death was sudden in 1, being shortly preceded by vertigo and dyspnea. The central nervous system was not examined at necropsy. Bell[10] found in his 7 cases of polycystic disease of the kidney in which death was not due to renal failure 2 instances of subarachnoid and 1 of cerebral hemorrhage. The description of vessels was limited to those of the kidney. The frequency of intracranial hemorrhage indicates that cerebral aneurysm may be considerably more frequent than is indicated by its actual demonstration.

Bilateral polycystic disease of the kidneys is now definitely established as due to a developmental defect. Virchow's[11] premise that the condition resulted from intrauterine nephritis is no longer tenable. Ribbert,[12] while appreciating the con-

4. Alpers, B. J.: Diffuse Progressive Degeneration of the Gray Matter of the Cerebrum, Arch. Neurol. & Psychiat. 25:469-505 (March) 1931.

5. Dunger, R.: Zur Lehre von den Cystenniere, mit besondere Berücksichtigung ihrer Heredität, Beitr. z. path. Anat. u. z. allg. Path. 35:445-509, 1904.

6. Fearnsides, E. G.: Intracranial Aneurysms, Brain 39:224-296, 1916.

7. Sieber, F.: Ueber Cystennieren bei Erwachsenen, Deutsche Ztschr. f. Chir. 79:406-507, 1905.

8. Coombs, C.: Polycystic Disease of the Kidneys, Quart. J. Med. 3:30-33, 1909-1910.

9. Atonna, C., and Morrissey, J. H.: Polycystic Kidneys, Ann. Surg. 84:846-854, 1926.

10. Bell, E. T.: Cystic Disease of the Kidney, Am. J. Path. 11:373-418, 1935.

11. Virchow, R., cited by Beckmann, O.: Zur Kenntnis der Niere, Virchows Arch. f. path. Anat. 11:121, 1856.

12. Ribbert, H.: Ueber die Entwicklung der bleibenden Niere und über die Entstehung der Cystenniere, Verhandl. d. deutsch. path. Gesellsch. 2:187-203, 1900.

genital origin, erroneously concluded that the cause was failure of fusion between the convoluted and the collecting tubules. Kampmeier[13] succeeded in demonstrating that the cause is failure of the normal atrophy of the first generations of the convoluted tubules—those which normally are not attached to the collecting tubules.

Congenital anomalies are notoriously prone to occur in combination, and the reporting of such situations presaged the embryonic evidence for their anomalous origin. Dunger[5] gathered from the literature twenty-four congenital anomalies which had been reported to occur in association with polycystic disease of the kidneys. The most remarkable combination of anomalies in cases of polycystic kidney was that reported by Rosenow[14] in 1911, virtually every system examined being involved. There were anomalies of the cardiovascular, gastroenteric and genitourinary systems, but, unfortunately, the nervous system was not studied. Bell[10] included in his report 3 instances of maldevelopment of the neural tube.

Previously Reported Cases of Intracranial Aneurysm and Congenital Polycystic Kidney

Author	Case No.	Age, Yr.	Sex	Site of Aneurysm	Aneurysm Ruptured or Unruptured
Dunger [5]	1	54	F	Left anterior cerebral artery...	+
Fearnsides [6]	2	53	M	Left anterior cerebral artery and anterior communicating artery	—
Katz, G., and Mühe, E.: Ztschr. f. Urol. 18:453-461, 1924	3	45	F	Right middle cerebral artery... Anterior communicating artery Right internal carotid artery and right middle cerebral artery	— + —
Snapper, I., and Forminej, P.: Acta med. Scandinav. 101:105-115, 1939	4	†	F	‡	+
	5	47	F	Right internal carotid artery and right middle cerebral artery	+
	6	48	M	Right middle cerebral artery...	+
O'Crowley, C. R., and Martland, H. S.: Am. J. Surg. 43:3-9, 1939	7	42	M	Right middle cerebral artery... Left middle cerebral artery (2)	+ —
	8	56	F	Anterior communicating artery	+
	9	27	M	Right middle cerebral artery...	+

† Age not given, but patient was married.
‡ Diagnosis made clinically; patient survived.

Since congenital polycystic kidney tends to occur in association with other anomalies and the same is true of cerebral aneurysm, it is not surprising that the two conditions should occur together. This occurrence is inductive evidence in favor of the congenital nature of the aneurysms associated with polycystic kidney.

It is true that hypertension and vascular disease might be expected to be present in cases of renal failure due to the renal lesions. Schacht[15] and Toulson and Wagner[16] reported the occurrence of hypertension in patients with congenital

13. Kampmeier, O. F.: A Hitherto Unrecognized Mode of Origin of Congenital Renal Cysts, Surg., Gynec. & Obst. 36:208-216, 1923.

14. Rosenow, G.: Polyzystisches Nierenrudiment bei Fehlen des Ureters und Vas deferens, appendikulärer Schwellkörper des Penis und zahlreiche andere Missbildungen bei einem 8 monatlichen Fötus, Virchows Arch. f. path. Anat. 205:318-334, 1911.

15. Schacht, F. W.: Hypertension in Cases of Congenital Polycystic Kidney, Arch. Int. Med. 47:500-509 (March) 1931.

16. Toulson, W. H., and Wagner, J. A.: Cystic Kidneys with Increased Blood Pressure, Bull. School Med. Univ. Maryland 26:177-184, 1942.

polycystic kidneys. Bell,[10] who limited his study of blood vessels to those of the kidneys, observed medial sclerosis in only 1 of 7 instances. However, in the present case the absence of the media could not conceivably be considered as the result of a degenerative process, and this viewpoint is further strengthened by the absence of degenerative changes in the media in other vessels. Moreover, thirteen weeks of extrauterine life—the duration of the infant's dependence on his own renal function—seems too short a time for an aneurysm to have developed on the basis of a vascular degenerative process. In view, then, of the age of the patient, the minuteness of the aneurysm and its origin from an area of defect in the media, the only tenable conclusion is that the aneurysm was congenital.

Forbus[1] first demonstrated the presence of a defect of the media at the point of origin of congenital aneurysms. He demonstrated the presence of such a defect at the bifurcations of the great vessels of the circle of Willis. Richardson and Hyland[2] confirmed this observation but indicated that the development of aneurysm is not entirely explained by the defect of the media. This viewpoint is supported by our observations, in which a similar area of defect of the media occurred diametrically opposite the origin of the aneurysm.

Bremer[17] recently demonstrated that congenital aneurysm may arise in still another fashion. In certain areas of the circle of Willis—notably about the anterior communicating artery—there occurs in the course of development of the arterial system a plexus of small arteries, almost all of which are destined to atrophy and disappear. Enlargement of the proximal end of such a member of a plexus, with degeneration of its distal end, can produce an aneurysmal sac. The presence of small vessels in the wall of an aneurysm is considered an indication of such an origin. The aneurysm described in this report cannot be considered to have such an origin, since it occurred at a bifurcation and no small vessels were included in its wall.

According to Bremer, the presence of the internal elastic membrane in the aneurysm in this case would not permit its classification as a true congenital aneurysm. This choice of terminology is unfortunate, since in the older literature a true aneurysm—aneurysma verum—was comprised of all three coats, whereas according to Bremer a true aneurysm is one in which the media and the elastica interna are lacking. Bremer cited Roux to the effect that the presence of the elastica interna depends on the relative strength of the pulse. Therefore the absence of the elastica interna in a given aneurysm may be due to either one of two situations: 1. The aneurysm may have developed before the formation of the elastica interna in the parent vessel, and if the aneurysmal wall was not subsequently affected by strong pulsations, the elastica may not have developed in the sac, even though this layer formed in the wall of the parent vessel. 2. The aneurysm may have developed after the parent vessel had an internal elastic membrane, and the aneurysmal wall may have included this structure; if, however, pulsations in the aneurysm were inadequate, the elastica interna may have subsequently disappeared. The classification of aneurysms as true congenital and spontaneous, "though due to conditions similar to those leading to congenital aneurysms," seems unwarranted, particularly when a variable structure, such as the elastica interna, represents the criterion for classification. This contention is borne out by the aneurysm described in this report—obviously, one of congenital type and yet containing a well developed internal elastic membrane.

17. Bremer, J. L.: Congenital Aneurysms of the Cerebral Arteries: An Embryologic Study, Arch. Path. **35**:819-831 (June) 1943.

CONCLUSIONS

There is a tendency for congenital polycystic kidney and cerebral aneurysm to occur in the same patient. This association may be more frequent than its actual demonstration indicates, since there is a high mortality rate due to intra-cranial hemorrhage in patients with polycystic kidney. Aneurysms of this type have been considered of congenital origin. The age of the patient in the case reported, the small size of the aneurysm and the demonstration of a defect in the media at the site of the aneurysm indicate the congenital nature of this aneurysm. The presence of internal elastic membrane in the aneurysmal wall is not considered an adequate criterion for the classification of an aneurysm as spontaneous.

1025 Walnut Street.
111 North Forty-Ninth Street.

DIFFUSE HYPERTROPHY OF THE CEREBELLAR CORTEX (MYELINATED NEUROCYTOMA)

REPORT OF A CASE

DONALD DUNCAN, Ph.D.
BUFFALO

AND

S. R. SNODGRASS, M.D.
GALVESTON, TEXAS

The following case is reported because of its intrinsic interest and the rarity of the condition, and as a possible aid in the future recognition and successful treatment of this disease. The original description of the condition is credited to Lhermitte and Duclos,[1] their paper appearing in 1920. Four cases have been reported since that time, 1 each by Schmidt,[2] Bielschowsky and Simon,[3] Barten[4] and Heinlein and Falkenberg.[5] In all cases, the patient exhibited signs and symptoms of an intracranial growth, and in each case an extensive area of hypertrophied cerebellar gyri was discovered. The abnormal areas were characterized microscopically by enlargement of the nerve cells, little or no reaction of the glia and myelination of the molecular layer. None of these patients was treated successfully, but Christensen[6] described a similar condition in which the patient was living and well one and one-half years after extensive removal of the abnormal cerebellar cortex. A comparative summary of the reported cases is given in the accompanying table.

REPORT OF CASE

History.—A white woman aged 27, married, entered the hospital complaining of headaches, unsteady gait and failing vision.

The patient had been married three years but had never been pregnant. For a year her husband had been known to have active pulmonary tuberculosis.

The family history was good, and there was no history of malignant disease or disease of the nervous system.

The patient's general health had always been good. When she was an infant, her head was noted to be large, and it had always been considerably larger than that of any other member of her family. When she was 2 years old her left index finger was crushed in a door, and soon a tumor appeared at the site of the injury. The tumor slowly increased in size and came to involve the index and middle fingers and the proximal portion of the ring

1. Lhermitte, J., and Duclos, P.: Sur un ganglio-neurome diffus du cortex du cervelet. Bull. Assoc. franç. p. l'étude du cancer 9:99, 1920.

2. Schmidt, M. B.: Ueber halbseitigen Riesenwuchs des Schädels und seine Beziehung zu Leontiasis und Osteitis fibrosa, Beitr. z. Anat., Physiol., Path. u. Therap. d. Ohres 23:594, 1926.

3. Bielschowsky, M., and Simon, A.: Ueber diffuse Harmartome (Ganglioneurome) des Kleinhirns und ihre Genese, J. f. Psychol. u. Neurol. 41:50, 1930.

4. Barten, H.: Eine seltene Fehlbildung des Kleinhirns (Ein Beitrag zur Frage der Ganglioneurome), Beitr. z. path. Anat. u. z. allg. Path. 93:219, 1934.

5. Heinlein, H., and Falkenberg: Beitrag zur Kasuistik der Ganglioneurome des Kleinhirns, Ztschr. f. d. ges. Neurol. u. Psychiat. 166:128, 1939.

6. Christensen, E.: Ueber Ganglienzellgeschwülste im Gehirn, Virchows Arch. f. path. Anat. 300:567, 1937.

finger. The fingers became a deep purple and were about twice the normal diameter. When she was 14 years old, this mass was removed by resection of the index and middle fingers and the adjacent portions of the metacarpal bones. There had been no recurrence of the lesion. ·The tumor is reported to have been a cavernous angioma.

For as long as the patient could remember, she had noted the presence of two scarcely palpable nodules in the occipital portion of her scalp. Without apparent cause, a year and a half before admission one of these nodules began to enlarge rapidly and within a month became a pulsating mass the size of a hen's egg. This mass was then removed, and it is reported also to have been an angioma. A few days after removal of the lesion from the scalp, the patient began to experience frontal and occipital headaches, which recurred with increasing frequency and severity. Shortly after the onset of the headaches she detected a continuous bruit in the right ear; she soon learned to stop the bruit temporarily by compressing the right side of her neck. Soon attacks of weakness began to occur, during which she would fall to the floor because of sudden and unexpected loss of strength in her legs; there was no loss of consciousness, nor were there convulsive movements. Eight months before admission diplopia appeared and persisted thereafter; at about this time failure of vision was noted, and this had gradually progressed to the point where she could not read the newspaper. Her gait became unsteady and staggering.' She complained of frequent attacks of numbness of her face and, to a lesser degree, of her body. Subsequently there had

Summary of the Reported Cases of Diffuse Hypertrophy of the Cerebellar Cortex with Myelination of the Molecular Layer

Author	Date of Report	Age, Yr.	Sex	Duration of Symptoms	Part of Cerebellum Involved	Other Data
Lhermitte and Duclos...	1920	36	M	1 year	Left hemisphere	Head injury in infancy
Schmidt.................	1926	45	M	....	Left hemisphere	Multiple congenital anomalies; malignant growth of parotid with metastasis
Bielschowsky and Simon	1930	20	F	2-3 years	Right hemisphere and vermis	Weight of brain 2,113 Gm.; 6 fingers at birth
Barten..................	1934	37	F	....	....	....
Heinlein and Falkenberg	1939	23	M	2-3 years	Vermis and right hemisphere	Severe head injury in childhood
Duncan and Snodgrass..	1943	27	F	1½ years	Left hemisphere and minute areas in the vermis and right hemisphere	Weight of brain 1,960 Gm.; multiple hemangiomas of fingers and scalp

been attacks in which for a few minutes her speech was unintelligible on account of inability "to control her tongue." Although vomiting was frequently associated with her headaches, her appetite was excellent, and she had gained 15 pounds (6.8 Kg.) during her illness.

Examination.—The patient was obese; she was 5 feet (152.4 cm.) in height and weighed 160 pounds (72.6 Kg.). There were no abnormalities of the skin, and general physical examination revealed nothing significant. The patient was well oriented; her mental powers appeared normal, and there was no disturbance of speech. The head was noticeably enlarged, and the frontal and parietal bosses were prominent. There were considerable stiffness of the neck and suboccipital tenderness. There was papilledema of 6 D. in the right ·eye and of 8 D. in the left; numerous hemorrhages and patches of exudate were noted in each eye, and the optic nerve heads were moderately pale. Visual acuity was 20/50 in the right eye and 20/100 in the left eye. The visual fields showed moderate concentric contraction. There was sustained coarse lateral nystagmus on her looking to either side. Diplopia was present on her looking to the right. The corneal reflexes were absent, and there was hypesthesia over the left side of the face. The gag reflex at times was absent on the left side of the pharynx, and sensation in this region was diminished at such times. The tongue protruded slightly to the right of the median line. There was no ataxia of the extremities, but inability to perform rapidly alternating movements was present bilaterally. The gait was reeling, and the patient could not walk without aid. She walked with the feet widely separated and progressed with rapid, short steps; there was a strong tendency to fall to the right. The abdominal reflexes were absent. The deep reflexes were absent in the upper and lower extremities on the left side but were abnormally increased on the right side. The plantar

responses were flexor. At times there appeared to be hypesthesia below the middorsal segments, being greater on the left side than on the right. As this sign was variable and inconstant, it was thought to be of hysterical nature.

Laboratory studies added little information of value. The spinal fluid was under a pressure of 400 mm. of fluid; the protein content, serologic reactions and cell count were normal. Roentgenograms of the skull showed increased convolutional markings and moderate decalcification and thinning of the dorsum sellae; this indicated a long-standing increase in the intracranial pressure.

Ventriculographic Study.—The history of previous operations for angioma and the subjective bruit suggested the possibility of such a tumor as the cause of the patient's symptoms. Although the presence of a cerebellar neoplasm seemed extremely probable, ventricular injection of air was carried out to make the diagnosis more certain. The injection was done with procaine anesthesia through bilateral posterior parietal perforator openings. The lateral ventricles were dilated, and 150 cc. of cerebrospinal fluid was replaced by air. Roentgenograms showed symmetric dilatation of the lateral and third ventricles (fig. 1 *A* and *B*). The aqueduct of Sylvius was kinked anteriorly in its middle portion, and there appeared to be slight anterior displacement of the fourth ventricle. The fourth ventricle was not visualized in anteroposterior projections. The roentgenographic changes corroborated the clinical diagnosis of cerebellar tumor.
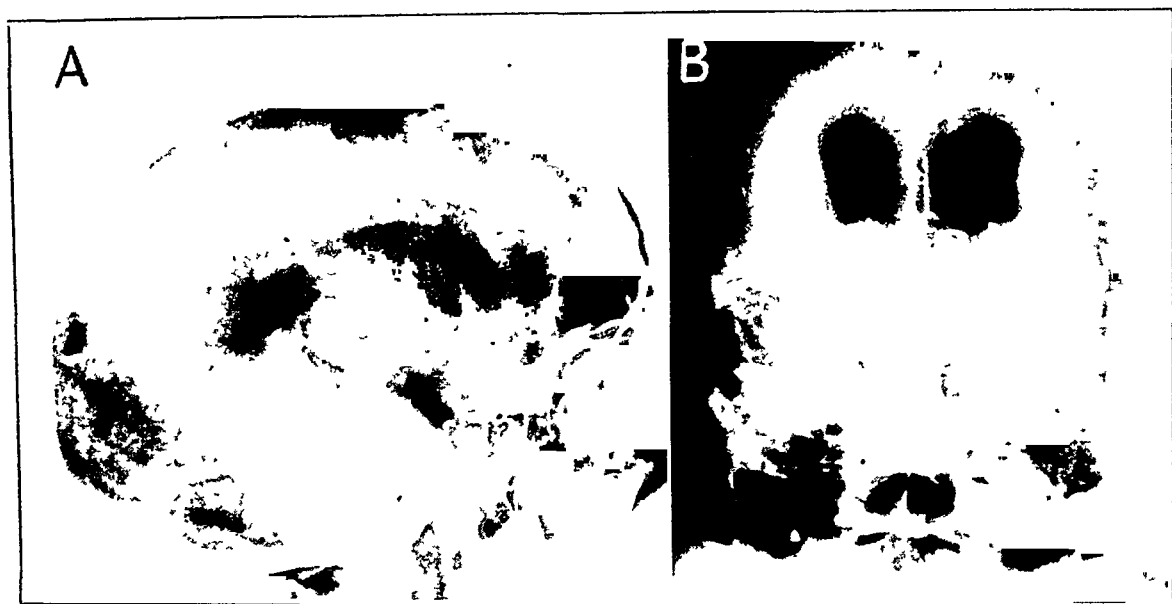
Fig. 1.—*A*, lateral ventriculogram, showing uniform dilatation of the lateral and third ventricles, kinking of the aqueduct and forward displacement of the fourth ventricle. *B*, anteroposterior ventriculogram, showing symmetric enlargement of the lateral ventricles and absence of lateral displacement.

Operation.—Bilateral suboccipital exploration was carried out the same day, with the patient under anesthesia induced with solution of tribromoethanol, supplemented with procaine. The occipital bone was greatly thinned, particularly on the left side. The cisterna magna contained air, but the fissure between the cerebellar hemispheres was displaced approximately 2.5 cm. to the right of the median line. The cerebellar tonsils were displaced into the upper cervical portion of the canal. They were released by laminectomy of the first cervical vertebra. The medulla and the upper cervical portion of the cord were seen to be distorted by displacement of the brain stem to the right. Except for an apparent considerable increase in size, there was no palpable or visible abnormality of the left cerebellar hemisphere. Exploration of the left cerebellopontile angle showed no tumor, and two incisions into the left cerebellar hemisphere failed to disclose a recognizable neoplasm. Although it appeared highly probable that the left cerebellar hemisphere contained a space-occupying lesion, the wound was closed in the usual manner. It was hoped that the additional space provided in the posterior cranial fossa by removal of the occipital bone would reduce the intracranial pressure sufficiently to afford the patient some relief. Partial resection of the left cerebellar hemisphere would have been preferable.

Course.—After operation the patient regained consciousness, but from the time of operation there was considerable elevation of temperature. The day after the operation she became disoriented; her temperature was extremely high, and she died approximately twenty-four hours after operation.

Necropsy.—Internal examination was limited to the contents of the cranium.

General Inspection: The body was obese, and the face, the trunk and, especially, the lower limbs were covered with more than the usual amount of dark hair. The areolas of the breasts were large, especially on the left side, and were deeply pigmented.

The head was large but well formed except for slight prominence of the occiput and frontal bosses. A transverse flap of bone was absent from the suboccipital region of the skull. There was no evidence of infection of the wound. A small amount of blood was present at the base of the brain and at the anterior tip of each frontal lobe.

Gross Examination of the Brain: The brain was very large, weighing 1,960 Gm., and was moderately edematous and congested. The left cerebellar hemisphere was slightly larger than the right and showed two transverse incisions extending to a depth of 4 cm. No surface indications of a cerebellar tumor could be seen, and no tumor was present along the cranial nerves. The vessels appeared normal. The lateral and third ventricles and the aqueduct of Sylvius were moderately and symmetrically distended. The floor of the third ventricle just behind the infundibulum was distended to form a thin-walled, rounded pocket, about 1 cm. in diameter. The brain was immersed in dilute solution of formaldehyde U. S. P. in preparation for further study.

The formaldehyde-hardened brain was inspected and then cut into thin slices. Careful examination of the cerebral hemispheres, the midbrain and the pons failed to reveal any abnormalities other than the unusual size and the hydrocephalus noted at autopsy. The medulla was deviated to the right and compressed from side to side. Sections of the right cerebellar hemisphere appeared normal, but in the left hemisphere abnormal areas were present. These areas consisted of an even enlargement of several adjacent gyri, the hypertrophy giving way abruptly to cortex of normal thickness. Several of these altered regions were noted, but they were not exactly localized. In them the cortex was approximately twice the normal thickness. Both the normal and the thickened cortex bordering the surgical incisions were blood stained and softer than surrounding areas; otherwise, no differences in color or consistency were observed at this time. On reinspection of the gross material after microscopic examination it was evident that the outer layer of the thickened cortex was whiter than normal.

Microscopic Examination: The cortex in the thickened areas showed profound alteration. Sections stained for myelin sheaths revealed an outer cortical layer containing great numbers of fine myelinated nerve fibers (fig. 2 A). This layer corresponded in position to the molecular layer of the normal cerebellum, which is practically free of myelin. Although the thickness and density of the outer myelinated layer varied greatly, and in places quite abruptly, the fiber pattern was uniform throughout. As illustrated in figure 2 D, the myelinated fibers were of fine caliber and coursed in two directions, at right angles' to each other; they either paralleled the surface or ran perpendicular to it. This arrangement is precisely that of normal granule cell axons, which ordinarily are unmyelinated except for a very few lying close to the Purkinje layer. Silver stains for axons revealed a large number of unmyelinated fibers intermingled with the myelinated ones and arranged in the same pattern.

In addition to the very large region of abnormality, minute areas of myelinated cortex were scattered throughout the cerebellum; one of these is indicated in figure 2 A and another, under a higher magnification, is shown in figure 2 C. Each of the twenty blocks of tissue taken from the two cerebellar hemispheres and from the vermis contained one or more of these abnormal areas.

As described in previous accounts, the medullary centers of the enlarged gyri were unusually narrow and contained few nerve fibers; however, nerve fibers were never entirely absent.

Stains for nerve cells showed that they were equally atypical (fig. 3). The most striking changes were numerous large nerve cells in the molecular layer, disappearance of a recognizable Purkinje layer and increased width of the granular layer, accompanied by a great increase in the size of its component cells. While they were numerous, large and variable as to number in any given area, the nerve cells of the molecular layer were nowhere collected into definite nests, nor were they confined to any one depth from the surface. In numbers and distribution they were probably similar to the basket and stellate cells of the normal cerebellum but were rendered much more conspicuous because of their size. Purkinje cells were not identified with certainty. Large and mature-looking neurons which looked much like Purkinje cells were scattered throughout the altered cortex; they differed in being somewhat larger and in not being confined to a single row along the outer border of the granular layer. Nevertheless, it was assumed that these cells represented the Purkinje type. In numbers, the predominant type was a medium-sized nerve cell with a few robust

Fig. 2.—*A,* parasagittal section of the inferior part of the left cerebellar hemisphere; × 1.7, *1* indicates a small isolated area of abnormal cortex, and *2,* a single normal folium surrounded by grossly altered cortex. Enclosed by a square is the area shown in *B. B,* a higher magnification (× 17) of the area indicated in *A.* Normal cerebellar cortex is seen at the left and abnormal cortex at the right of the figure. *C,* a small, isolated area of abnormal cerebellar cortex, similar to that indicated by *1* in *A* and found in all parts of the cerebellum; × 17. *D,* a high power view of the molecular layer, from the area shown in *C;* × 300. Here, *p* marks the pia, and *g,* the granular layer. Note the large numbers of fine myelinated fibers running either parallel with, or at right angles to, the surface; this pattern is characteristic of normal granule cell axons. Myelin sheath stain.

dendrites and a moderate amount of cytoplasm containing dustlike particles of Nissl substance. As indicated in figure 3 *A*, the outer cells of the granular layer were larger in general than the cells nearest the medullary substance. In places two distinct zones were apparent—an inner zone composed of cells differing little, if any, from the ordinary granule cells and an outer zone of enlarged cells. This feature was most conspicuous where normal and abnormal cortex met, and it disappeared in many regions owing to a rather uniform enlargement of all cells in the granular layer.

Prolonged and repeated examinations were made for mitotic and amitotic figures, without any being found, nor were other signs of hyperplasia or cellular immaturity observed. Bizarre
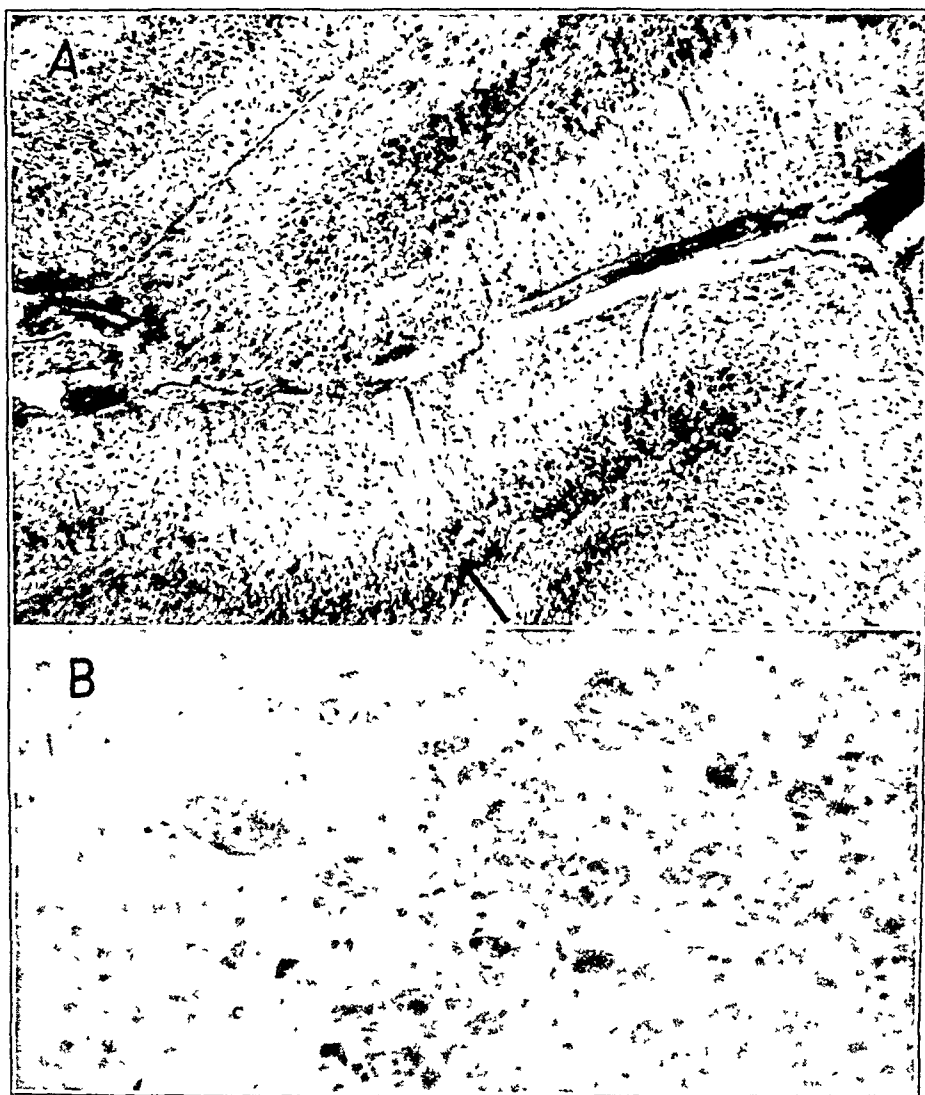
Fig. 3.—*A*, photomicrograph of a Nissl-stained section from the major abnormal area; × 40. Note the large scattered nerve cells in the molecular and granular layers and the disappearance of the usual cell pattern. Separation of the granular layer into a distinct inner (small cells) and outer (large cell) zone is indicated by the arrow. *B*, a high power view of a Nissl preparation, illustrating the most typical pattern in the granular layer of the abnormal cortex; occasional large cells of Purkinje type and numerous small and medium-sized nerve cells are present. × 600.

and degenerative cell forms were missing, also. Occasional vacuolated cells and some examples of disproportion in the size of the nucleus to that of the cell were the only features noted that could be interpreted as signs of degeneration or dysplasia. Vascular changes were inconspicuous and consisted of some increase in the size, and perhaps the number, of penetrating vessels and a few perivascular accumulations of basic-staining globules. These bodies

were mentioned in previous accounts and have been called pseudocalcareous bodies by Bielschowsky and Simon. There were, of course, evidences of recent trauma due to the operation.

No free fat was seen in sections of the cerebellum stained with scarlet red. Successful impregnations of the various forms of neuroglia cells showed no departure from the usual pictures encountered in normal postmortem material. The cerebellar nuclei and peduncles were normal. The lower part of the medulla was distorted, and partial demyelination of the right pyramid was observed in myelin-stained sections. Considerable free fat was seen in this pyramid, and a slight amount was noted in the left lateral reticular formation. Sections from various levels of the brain stem above the lower portion of the medulla appeared entirely normal. Likewise, sections from all parts of the forebrain were devoid of abnormal features other than the dilated ventricles. It was concluded that the histopathologic process was confined to the cortex of the cerebellum. Here the principal region affected was the inferior surface of the left hemisphere, with additional minute areas of hypertrophy scattered throughout the cortex.

COMMENT

The histologic features of diffuse hypertrophy of the cerebellar cortex have previously been described in considerable detail. In particular, the description of Bielschowsky and Simon leaves little unsaid as far as could be determined from study of the present specimen. Nevertheless, one receives the impression that the true nature of the abnormal nerve cells has not been understood. In none of the descriptions is there a clearcut statement ascribing the great majority of the abnormal cells to hypertrophy of the granule cells. Such is considered to be their origin in the present case, as the location of the enlarged cells, and especially the arrangement of their axons, can scarcely lead to any other conclusion. This explanation assumes only that all parts of the granule cell have enlarged, with the following accompanying changes: (1) The nucleus is more vesicular, and the nucleolus is more prominent; (2) the cytoplasm is greatly increased and contains discernible Nissl substance; (3) the dendrites are much thicker, and (4) the axon is greatly increased in diameter and has acquired a visible myelin sheath.

The appearance of a myelin coating on the enlarged axis-cylinders is quite in accord with histologic and physical observations[7] indicating a critical diameter above which myelin is visible and below which the sheath is refractive to stains for myelin. Any other explanation for most of the abnormal cells would require the assumption of an origin from neuroblasts in great numbers, a profound alteration of other normal cell types, such as the Purkinje and basket cells, or intense multiplication of a rare and unrecognized type. While it it is impossible to exclude these possibilities entirely, all of them seem far less likely than simple enlargement of a cell type that conforms to the abnormal cells in all respects except size.

The sparsity of nerve fibers in the medullary zone of the abnormal region has been noted by all observers, without conclusions as to its meaning. In previous descriptions the condition is spoken of as a loss of fibers, but a relative reduction, due to the increased size of the affected folia, may also explain this feature. Such an explanation is supported by the absence of indications of myelin degeneration and the fact that some myelinated fibers are noted in the most attenuated parts of the medullary layer.

The only feature we hesitated to explain on the basis of simple hypertrophy of normally occurring nerve cells of the cerebellar cortex is the number and size of the cells in the molecular layer. At first sight, they were so conspicuous that it seemed necessary to call on some additional factor to account for their

---

7. Duncan, D.: A Relation Between Axon Diameter and Myelination Determined by Measurement of Myelinated Spinal Root Fibers, J. Comp. Neurol. **60**:437, 1934. Schmitt, F. O., and Bear, R. S.: The Optical Properties of Vertebrate Nerve Axons as Related to Fiber Size, J. Cell. & Comp. Physiol. **9**:261, 1937.

presence, but considerable study of the stellate cells in Golgi preparations of normal adult material strongly suggested that the incidence of such cells is sufficient to account for the number of large cells present in the outer layer of the tumor. With this possible exception, one can account for the histologic features of this condition by assuming a considerable increase in size on the part of most of the neurons present. Whether in the present case the abnormal growth occurred slowly, and over a long period, or with comparative rapidity during the last years of the patient's life cannot be answered with certainty, but the complete absence of symptoms referable to the cerebellum until eighteen months before death is strongly suggestive of the latter alternative.

This condition has been designated as a tumor of the brain, although the characteristic feature of hyperplasia is lacking. Regarded as a tumor, the abnormality finds its place at one extreme of the variations displayed by growths arising from neural ectoderm, with the undifferentiated hyperplastic types at the other. Placed with the cerebral tumors, the specimen is probably best defined as a myelinated neurocytoma, or gangliocytoma, the latter term being the one used in the classification proposed by Wolf and Morton.[8] Less accurately, it might be included under the more usual term of ganglioglioma, but such a designation is misleading, owing to the lack of any evidences of abnormality on the part of the glia. Undoubtedly, the present series of cases must receive a considerable number of additions before a precise terminology can be attempted with reasonable assurance of correctness. While tumors of this type seem to constitute a distinct entity, they are closely related to certain other cerebellar abnormalities and have some features in common with still others. One of the tumors described by Christensen resembled the myelinated form in nearly every respect but lacked the characterizing myelin. A case reported by Förster and Gagel[9] was also similar, but the peculiar distribution of the neural elements and the presence of localized accumulations of nerve cells led these authors to postulate a disturbance in growth superimposed on a congenital malformation. In other accounts both the glia and the nerve cells were said to be involved, and in many instances it is difficult to decide whether the condition was a tumor or a form of tuberous sclerosis.

No explanation is offered for the remarkable picture in the present case. The number of known instances of the lesion is too small to permit any generalizations as to age, sex, associated anomalies or predisposing signs, but it should be noted that in 2 cases excessive weights of the brain were recorded—2,113 Gm. in 1 case and 1,960 Gm. in another—and that tumors in other parts of the body are mentioned in 2 of the cases.

SUMMARY

A case of diffuse hypertrophy of the left cerebellar cortex leading to signs and symptoms of a cerebellar neoplasm is described. Histologically, the growth was composed of adult neurons arranged in a nearly normal pattern, but with the individual elements greatly enlarged. Most, if not all, of the enlarged cells appeared to be derived from the granule and the stellate cells of the cerebellum.

University of Buffalo, Buffalo.
John Sealy Hospital, Galveston, Texas.

8. Wolf, A., and Morton, B. F.: Ganglion Cell Tumors of the Central Nervous System, Bull. Neurol. Inst. New York 6:473, 1937.

9. Förster, O., and Gagel, O.: Ein Fall von Gangliocytoma dysplasticum des Kleinhirns, Ztschr. f. d. ges. Neurol. u. Psychiat. 146:792, 1933.

COMBINED CONVULSIVE THERAPY AND PSYCHOTHERAPY OF THE NEUROSES

JOHN D. MORIARTY, M.D.

AND

ANDRE A. WEIL, M.D.

CONCORD, N. H.

In psychiatry the factor of time has been a difficult obstacle to surmount. In the past few years insulin, metrazol and, finally, electric shock therapy have shortened the period of hospitalization of patients with the major psychoses.[1] Unfortunately, the problem of the neurotic patient, who requires much individual effort and consideration, has received relatively little attention in this respect.[2] Only a few studies of the application of shock treatment to the neuroses have been made.

A fairly comprehensive survey of the literature in regard to convulsive therapy of the neuroses discloses the following facts: Fourteen authors[3] have given the results of the treatment for all types of neuroses, a total of 130 patients being represented. In 36 patients (28 per cent) the disease was described as cured or in remission; in 80 patients (64 per cent) the condition was said to be improved, and in only 14 patients (11 per cent) was the condition not improved or were the results questionable. In addition, there were a number of reports of poorly defined disorders, with such designations as "depression" or "depressed obsessive states"[3l] and "chronic tension states."[2b] For the sake of accuracy, the figures for these con-

1. Ross, J. R., and Malzberg, B.: A Review of the Results of the Pharmacological Shock Therapy and the Metrazol Convulsive Therapy in New York State, Am. J. Psychiat. 96:297 (Sept.) 1939. Stewart, B.: Present Status of Shock Therapy in Neuropsychiatry with Special Reference to Prevention of Complications, Bull. Menninger Clin. 6:15 (Jan.) 1942. Weil, A. A.: The Modern Prognosis and Therapy of Schizophrenia (Dementia Praecox) from the Standpoint of the General Practitioner, J. Maine M. A. 31:99 (April) 1940.

2. (a) Sagebiel, J.: Shock Therapy in the Neuroses, Ohio State M. J. 35:385 (April) 1939. (b) Shapiro, H. D., and Freeman, W.: Shock Therapy (Insulin and Metrazol) in the Neuroses, M. Ann. District of Columbia 8:65 (March) 1939. (c) Smith, H. M.: Hypoglycemic Therapy, J. A. M. A. 108:1959 (June 5) 1937.

3. (a) Cheney, C. O.; Hamilton, D. M., and Heaver, W. L.: Metrazol as an Adjunct to Treatment of Mental Disorders, Psychiatric Quart. 15:205 (April) 1941. (b) Cook, L. C., and Ogden, W.: Cardiazol Convulsion Therapy in Non-Schizophrenic Reaction States, Lancet 2:885 (Oct. 15) 1938. (c) Cossa and Bougeant: Results of the Treatment of Psychoses with the Methods of Sakel and Meduna, Paris méd. 1:247 (May 18-25) 1940. (d) Furst, W., and Stouffer, J. F.: The Electrical Shock Treatment of Psychoses, Arch. Neurol. & Psychiat. 46:743 (Oct.) 1941. (e) Good, R.: Convulsive Therapy in War Psychoneurotics, J. Ment. Sc. 87:409 (July) 1941. (f) Impastato, D. J., and Almansi, R.: The Electric Fit in the Treatment of Mental Disease, Arch. Neurol. & Psychiat. 47:510 (March) 1942. (g) Low, A. A.: The Present Status of the Shock Treatment of the "Functional" Psychoses, Illinois M. J. 75:169 (Feb.) 1939. (h) Meggendorfer, F.: Electric Shock Treatment of Psychoses, Deutsche med. Wchnschr. 66:1155 (Oct. 18) 1940. (i) Myerson, A.: Experience with Electric-Shock Therapy in Mental Disease, New England J. Med. 224:1081 (June 26) 1941. (j) Schaechter, A.: Pentamethylenetetrazol in Therapy of Depressive States, Gyógyászat 77:162 (March 14) 1937. (k) Smith, L. H.; Hughes, J.; Hastings, D. W., and Alpers, B. J.: Electroshock Treatment in the Psychoses, Am. J. Psychiat. 98:558 (Jan.) 1942. (l) Zeifert, M.: Metrazol Remission in Severe Obsessive-Compulsive Neurosis of Twenty-Five Years' Duration, J. Nerv. & Ment. Dis. 92:290 (Sept.) 1940. (m) Sagebiel.[2a] (n) Shapiro and Freeman.[2b]

ditions are not included in the foregoing percentages, although they appear to be in agreement with the general pattern of results. Most of the authors made passing reference to psychotherapy in conjunction with shock treatment but gave the latter the major emphasis. A notable dissent was offered by Shapiro and Freeman,[2b] who submitted the opinion that probing psychotherapy may be harmful. It may be mentioned that of these fourteen authors, few dealt exclusively with neurotic patients; most were concerned primarily with psychotic patients and gave the results for neurotic patients as an appendix.

From this survey two striking conclusions can be drawn: First, the results of the various convulsive treatments of the neuroses are almost uniformly encouraging—better even than the results for most of the major psychoses. Second, the method has been applied by most investigators only grudgingly to the neuroses, and as a last resort, being limited for the most part to patients with stubborn and chronic conditions. Paradoxically, when shock therapy has been employed, the importance of psychotherapy has receded into the background.

It has been argued that convulsive treatment is too drastic for the neuroses. There was some justification for this view when metrazol was the agent used. However, since electric shock therapy has supplanted metrazol shock, convulsive therapy can be administered with virtually no major risks and few minor ones.[4] In fact, electric shock therapy is practicable for outpatient service.[31] We now produce convulsions exclusively with an electric shock apparatus which delivers a unidirectional current and with which small amounts of current, measured in milliampere seconds, are sufficient. This type of implement has been fully described by Friedman.[5]

We have found this apparatus very satisfactory, in that the margin of safety seems to be extremely great and the unpleasant after-effects of treatment are negligible. Probably any other standard instrument would be as satisfactory. The important therapeutic principle is the production of a quick convulsion with the minimal amount of current.

In treating neurotic patients with convulsive therapy we noticed rapid improvement in the majority. However, as we went on with the treatment, we noted that this improvement was frequently not maintained if no effort was made to resolve the personality conflicts by psychotherapy. Patients treated with shock therapy alone gave one the impression that the project was half completed. Only after such a patient was stabilized by means of psychotherapy did one achieve a feeling of having filled in the essential details. On the other hand, it should be emphasized that in another group of our patients treated with psychotherapy alone the results were disappointing until the additional lever of convulsive therapy was applied. Whenever possible, we employed an analytic form of psychotherapy, in the broader sense of the term, in order that the patient might gain insight.

We have been interested in evolving a practical procedure of treatment of the neurotic patient, designed to achieve the maximum result, rather than in comparing various therapeutic procedures by elaborate statistical studies. We have employed combined convulsive treatment and psychotherapy with a total of 20 patients, with the results indicated in the accompanying table.

4. Kalinowsky, L., and Barrera, E.: Electric Convulsion Therapy in Mental Disorders, Psychiatric Quart. **14**:719 (Oct.) 1940. Ebaugh, F. G., and Johnson, G. S.: Electrically Induced Convulsions in the Treatment of Mental Disorders, Am. J. M. Sc. **203**:147 (Jan.) 1942.
    5. Friedman, E.: Unidirectional Electrostimulated Convulsive Therapy, Am. J. Psychiat. **99**:218 (Sept.) 1942.

In summarizing this table, we find that of the total of 20 patients, the condition was considered to be in remission in 10 (50 per cent), to be much improved or improved in 9 (45 per cent) and to show questionable improvement in 1 (5 per cent). All of the patients with remissions have made a satisfactory adjustment since leaving the hospital. None of the group has had to remain in the hospital.

Data on Results of Combined Convulsive Treatment and Psychotherapy in Twenty Patients

Patient	Age, Yr.	Type of Neurosis	Duration of Illness	Type of Psychotherapy	Shock Treatments No.	Type	Results
Females							
T. M.	26	Hysteria	Since childhood	Analytic; positive persuasion	2	Metrazol	Remission on discharge; 1 yr. later: patient "greatly improved"
K. P.	38	Anxiety hysteria	6 mo.	Positive persuasion; reeducation	3	Electric shock	Remission on discharge
C. O.	41	Anxiety hysteria	6 yr.	Positive persuasion; reeducation	4	Electric shock	Remission on discharge
H. F.	26	Anxiety hysteria	1 yr.	Analytic; positive persuasion	5	Electric shock	Improvement; patient at home
Z. M.	48	Anxiety neurosis	2 yr.	Analytic; reeducation	6	Metrazol	Remission on discharge; 1 yr. later: patient "well"
H. C.	40	Neurasthenia	4 yr.	Analytic	6	Electric shock	Remission on discharge
H. G.	28	Neurasthenia	15 yr.	Analytic; reeducation	3	Electric shock	Patient left hospital much improved
J. H.	55	Neurasthenia with involutional coloring	2 yr.	Suggestion; reeducation	6	Electric shock	Improvement on discharge
B. L.	38	Psychasthenia	10 yr.	Positive persuasion; reeducation	5	Electric shock	Remission on discharge; 6 mo. later: patient "well"
C. H. H.	33	Psychasthenia	1 yr.	Analytic	6	Metrazol	Improvement on discharge; 1 yr. later: patient "adjusting well"
M. K. S.	23	Psychasthenia	6 mo.	Analytic; reeducation	4	Metrazol	Remission on discharge; 1 yr. later: patient "well"
M. K.	39	Psychasthenia	1 yr.	Positive persuasion; reeducation	4	Electric shock	Remission on discharge; returned home to take care of family
H. T.	39	Psychasthenia	2 yr.	Positive persuasion; reeducation	5	Electric shock	Patient much improved; returned home
E. M.	51	Reactive depression	2 mo.	Positive persuasion; reeducation	4	Electric shock	Remission on discharge; 6 mo. later: patient "well"
R. A.	20	Reactive depression	2 mo.	Analytic; reeducation	3	Electric shock	Remission; patient resumed work immediately
Males							
H. N.	42	Anxiety hysteria	22 yr.	Analytic; hypnotism	15	Electric shock	Patient much improved; went to work
J. W.	21	Psychasthenia	Since childhood	Analytic	9	Electric shock	Patient improved; working
J. H.	65	Psychasthenia with depr. col.	6 mo.	Positive persuasion	6	Electric shock	Patient improved on discharge; 6 mo. later: "well"
C. L.	36	Mixed type	5 yr.	Positive persuasion; reeducation	2	Electric shock	Questionable improvement; patient on parole
M. H. P.	41	Mixed type	17 yr.	Analytic; reeducation	4	Electric shock	Patient much improved; left hospital to go to work

As a control study we studied a consecutive series of 46 neurotic women and 33 neurotic men who were admitted to this hospital during the seven year period from 1934 to 1941. While here, these patients received orthodox treatment for the neuroses, including psychotherapy, but no form of shock therapy. All were discharged from the hospital. Only 7 per cent were considered to be recovered on discharge or to have a remission of the disease; the condition of 71 per cent was much improved or improved; and that of 22 per cent was not improved.

It should be noted that, in contrast to the number of treatments required for the psychoses, only four to six convulsive treatments are needed for the neuroses. Three illustrative cases follow.

CASE 1.—*Hysteria.*

T. M., a housewife aged 26, was first admitted to the hospital after a theatrical gesture of suicide. Her husband had been awakened by her loud screams and had found her with a glass of iodine generously diluted with water, crying that she meant to drink it but was "afraid that it would hurt."

As a child the patient had been strongly inhibited by excessively rigid, highly neurotic parents. About the time of adolescence she began to show occasional outbursts against restriction by violent yelling and weeping. Six months before admission she gave birth to a normal baby but was never able to care for it properly. On the slightest provocation she had stormy tantrums, using this method to cow her simple, passive husband completely.

In the hospital the patient's reactions continued to be characterized by emotional instability and immaturity. Active analytic psychotherapy was instituted, and a vast number of traumatic experiences were elicited. Most of them were of a frankly sexual nature and represented the childish explorations of an ignorant, but not unintelligent, girl. The patient improved somewhat but still showed resistance to acceptance of responsibility. The "will to get well" was hard to stimulate. Consequently, two convulsvie treatments with metrazol were administered, with rapid improvement. The patient showed increasing zest for living and participated with a much better attitude in the psychotherapeutic situation. She left the hospital with increased resources.

Follow-Up Studies.—A year later the patient showed a much more mature attitude and had made a better social adjustment at home than at any time before her hospitalization.

CASE 2.—*Psychasthenia.*

M. K. S., a student nurse aged 23, single, was admitted (voluntarily) with complaints of headaches, insomnia, lassitude and nervousness.

As a girl she exhibited strong strivings for recognition, coupled with feelings of frustration and inadequacy. After one year's study of dramatics she entered nursing school. Rather to her surprise, she made a good adjustment for the first two years.

However, shortly after her return from an affiliated period of training at a hospital for mental disease, she became apprehensive and oppressed by the fear that she would make a mistake in the operating room or in administering medicaments. Concomitantly, complaints of fatigue, insomnia and headache developed.

During the first part of her stay in the hospital many psychodynamisms were uncovered by analytic psychotherapy, but, despite intensive treatment, she remained rather listless and only passively cooperative. She stated that intellectually she could grasp many factors in her disorder but that emotionally she seemed unable to react adequately. The core of her neurosis seemed to be a love affair with a married physician, about which she had many feelings of guilt.

After one convulsive treatment, induced by metrazol, the patient showed marked improvement in emotional tone, becoming energetic and cheerful. She now cooperated actively in the psychotherapeutic sessions and for the first time expressed a strong desire to continue nursing. Three more shock treatments were given to guard against relapse. The patient left the hospital free from symptoms and resumed her training.

Follow-Up Study.—The patient completed training and was well over a year later.

CASE 3.—*Psychoneurosis, mixed type.*

M. H. P., a farmer and laborer aged 41, was basically somewhat immature, especially in his affectivity. He was always inclined to worry a great deal, even about other people's troubles.

After an appendectomy in 1925, he underwent an acute neurotic episode, characterized by various hypochondriacal ideas, tension and depression. He had to be hospitalized twice in other institutions (1925 and 1926) and never showed complete recovery thereafter.

For the past three years he had exhibited increased depression and apprehension, associated with hypochondriacal trends, severe tension states and insomnia, and had pronounced feelings of inferiority, especially in regard to his sexual capacity. After receiving electric shock stimulation, he showed definite improvement in emotional tone. He cooperated wholeheartedly in analytic psychotherapy, showed increased interest in his environment and demanded a higher grade of occupational therapy.

He left the hospital after only seven weeks' stay, all acute neurotic manifestations having disappeared. He stated on his release that he had not felt so well for many years; he resumed work immediately.

COMMENT

It has been pronounced [6] that, theoretically, all of the neuroses are completely curable. However, actual practice falls considerably short of this ideal goal. This is especially true when intensive and long-continued therapy cannot be given, e. g., in state hospital practice. In our previously mentioned control study the average period of hospitalization for the neurotic male patient was found to be seven months and that for the neurotic female patient nine months. This is in line with the results of recent studies at the New York Hospital, Westchester Division, of 100 psychoneurotic men [7] and 100 psychoneurotic women,[8] which indicated that with psychotherapy alone the average length of hospitalization was eight and a half months for men and nine months for women. While the period of hospitalization of the patients in the present series varied considerably, none needed to remain in the hospital more than eight weeks after shock therapy was started.

It is our clinical impression that the total effect of combined shock treatment and psychotherapy is greater than the sum of its component parts. Thus, with shock therapy alone one first observes in the neurotic patient almost immediate improvement in eating and sleeping, two of the most basic psychophysiologic functions. Further, there occurs a bettering of emotional tone, with leavening of the depressive features and conquering of listlessness. How this is accomplished is by no means certain, but the fact remains that in the vast majority of patients it is accomplished. We are convinced that the mechanisms transcend any conscious process. From a psychobiologic standpoint, the investigation of Clark and Norbury [9] tends to support the premise that, in general, shock therapy achieves its results by stimulating the most basic drives for self preservation. Unconsciously the experience of dying and resurrection may be involved. It is possible even that the improvement in emotional tone may be brought about primarily by purely physiologic mechanisms, through the medium of subcortical stimulation. At any rate, the "will to get well" is generated and an attitude of active cooperation is fostered. The harmful, vicious circle of the "repetition compulsion" and of "rut thinking" tends to be broken. It should be emphasized that before these changes occur many neurotic patients are more or less unreceptive to psychotherapy. A primary feature of almost every neurosis is the depressive element, and this presents one of the principal obstacles to psychotherapy.

Conversely, it should be stressed that insight is ordinarily not gained through shock therapy alone; this must be derived from psychotherapy. Frequently analytic psychotherapy is invaluable in laying the groundwork for shock treatment; "psychagogic" methods (Kretschmer), including positive persuasion and reeducation, may be utilized for the after-treatment.

In contemplating the tremendous problem of the war neuroses now developing, one is impressed by the need for less time-consuming therapy. On the assumption of certain strong similarities between neuroses in civilian life and many of the neuroses in military life, it is safe to infer that this form of treatment may be of benefit in management of the subacute and chronic forms of war neuroses. Among our more recently treated patients, not reported on in the present paper,

6. Menninger, K. A.: The Human Mind, New York, Alfred A. Knopf, 1930, p. 136.

7. Hamilton, D. M., and Wall, J. H.: Hospital Treatment of Patients with Psychoneurotic Disorders, Am. J. Psychiat. **98**:551 (Jan.) 1942.

8. Hamilton, D. M.; Varney, H. I., and Wall, J. H.: Hospital Treatment of Patients with Psychoneurotic Disorders, ibid. **99**:243 (Sept.) 1942.

9. Clark, S. N., and Norbury, F. G.: A Possible Role of the Element of Fear in Metrazol Therapy, Dis. Nerv. System **2**:196 (June) 1941.

we have a soldier with severe psychasthenia which developed at camp and which persisted after his medical discharge from the army. This patient made an excellent response to combined electric shock therapy and psychotherapy. Previously, however, he had been entirely resistant to psychotherapy alone, given before his coming to this hospital.

SUMMARY AND CONCLUSIONS

Twenty neurotic patients in the New Hampshire State Hospital who received a combination of convulsive treatment and active psychotherapy have been studied. This study was undertaken primarily to evolve a practical procedure of treatment rather than to make a statistical comparison of different types of treatment.

The usual procedure of choice is first analytic psychotherapy, followed by four to six electric shock treatments and, finally, by efforts at reeducation.

In 50 per cent of our series of patients· the disease was considered to be in remission; in 45 per cent the condition was much improved or improved, and in 5 per cent it was questionably improved.

The period of hospitalization for treatment of the neuroses is definitely shortened.

Follow-up studies indicated a satisfactory adjustment and gain in inner resources in the vast majority of our patients. All were able to leave the hospital.

The conception of the healing mechanism is as follows: Shock therapy prepares the ground for psychotherapy by improving the affective tone, fostering active cooperation and tending to overcome the "repetition compulsion." Psychotherapy permits the patient to gain understanding and inner fortitude, as a guard against relapse.

DISCUSSION

LLOYD H. ZIEGLER, Wauwatosa, Wis.: Dr. Moriarty and Dr. Weil have impressed me favorably with their combined use of an older and a newer method of treatment, despite discouraging reports from the literature which they reviewed. Some of their diagnoses might be questioned. Word label diagnoses in psychiatry may not be meaningful. They differ notoriously from clinic to clinic. The authors got at the gist of the difficulties in human nature, however, as demonstrated in their brief case histories. The important thing is that they gave their patients therapeutic opportunities.

There has been a growing tradition that shock does not help neurotic patients. But there was a tradition many years ago that the earth was flat; experience proved it to be otherwise. I have not treated neurotic patients by the methods outlined. I have seen many patients with mild depressions, who were not frankly psychotic, recover with shock treatment and psychotherapy of one kind or another. Many of these patients had been called "merely neurotic." The distinction between a neurosis and a psychosis is often theoretic and a matter of academic controversy. The authors are to be commended on their slightly different use of shock as one facility for the cure of patients, tradition to the contrary.

New Hampshire State Hospital.

PERCEPTUAL-MOTOR PATTERNS FOLLOWING BILATERAL PREFRONTAL LOBOTOMY

LIEUTENANT GEORGE W. KISKER
ADJUTANT GENERAL'S DEPARTMENT, ARMY OF THE UNITED STATES

In an investigation of the behavioral sequelae of bilateral prefrontal lobotomy in treatment of the psychoses,[1] it occurred to me, in the light of the fact that the frontal lobes are connected not only with other cortical areas but with diencephalic, pontile and cerebellar complexes, that these subordinate neural ramifications might possibly be reflected in a neurodynamic reorganization of the motorium of the patient who has been subjected to operation, as well as of the so-called higher psychologic systems involving emotionality, attitudes and intellection. It was recognized that such reorganization must be of a subtle, implicit kind, since previous reports of postoperative sequelae, as well as my own observations, did not reveal overt motor phenomena of a consistent or significant nature. There remained the possibility, however, of the presence of masked changes which might be detected provided appropriate technics of measurement and evaluation were employed. While it would be difficult to say what effect implicit motor readjustments have in the important matter of therapeusis, there is no question that even minor motor repercussions assume an important aspect when related to the problem of fundamental cerebral dynamics. Evidence has pointed to the direct relation of the cytoarchitecture of the frontal lobes to motor activity. Much of the early work in extirpation of the animal brain indicated that lesions in the frontal lobe are likely to be accompanied by disturbances of the motorium. Jacobsen[2] showed clearly that one of the characteristics of animals so treated is failure in the organization of movement, and, more recently, Richter and Hines[3] reported further studies on the motor activity of lobectomized animals. When only a small portion of the frontal lobe is removed from the brain of the rat, the animal becomes extremely hyperactive, sometimes running over forty-eight miles (77.2 kilometers) in twenty hours. Similarly, monkeys with areas 9 and 10 removed become extremely active, while cats with the frontal poles excised literally run themselves to death. In an investigation along this same line, Kennard, Spencer and Fountain[4] ablated portions of areas 8 to 12 of Brodmann in monkeys and noted an increase in purposeless, repetitive activity. Significantly, the hyperactivity is influenced by visual factors, since it disappears both in the dark and after enucleation of the eye and occipital lobectomy. The interdependence of space-time correlates and perceptual structure, as they relate to motor activity, is shown clearly in this mechanism.

1. Kisker, G. W.: (a) Remarks on the Problem of Psychosurgery, Am. J. Psychiat. **100**:180, 1943; (b) The Behavioral Sequelae of Neurosurgical Therapy, J. Gen. Psychol., to be published; (c) Psychopathological and Neuropathological Implications of Bilateral Prefrontal Lobotomy, J. Nerv. & Ment. Dis., to be published.

2. Jacobsen, C. F., cited by Bucy, P. C.: Frontal Lobe of Primates: Relation of Cytoarchitecture to Functional Activity, Arch. Neurol. & Psychiat. **33**:546 (March) 1935.

3. Richter, C. P., and Hines, M.: Increased Spontaneous Activity Produced in Monkeys by Brain Lesions, Brain **61**:1, 1938.

4. Kennard, M. A.; Spencer, S., and Fountain, G., Jr.: Hyperactivity in Monkeys Following Lesions of the Frontal Lobes, J. Neurophysiol. **4**:512, 1941.

A number of studies of lesions of the frontal region of the human brain and of cerebral neoplasms have emphasized the importance of motor changes. Goldstein [5] described a large number of motor signs accompanying such lesions, including sudden attacks of a chronic character, as well as more permanent symptoms related to disturbances in maintenance of equilibrium. Tumors of the frontal lobe are frequently related to increased psychomotor activity and generalized restlessness. Of course, the functional localization of motor activity in the human brain has been more clearly differentiated than in the animal brain. My interest at this time is directed toward the prefrontal area of the frontal lobe. This area is located anterior to the region specifically designated as the motor projection area.

In view of the general consensus that frontal and prefrontal lesions are frequently observed in conjunction with disturbed motor activity, my associates and I attempted to verify, both experimentally and on the basis of general observation, the degree of such disturbance present in our series of lobotomized patients.

METHOD AND MATERIAL

The experimental devices used in our work included the Luria tremographic technic, a series of visual-motor tests and, finally, incidental tests of the organization of the motor schema. The subjects used in these experiments consisted of 20 psychotic patients who were subjected to bilateral prefrontal lobotomy for therapeutic purposes. The operations, and the subsequent experimental and observational programs, were carried out from September 1941 to September 1942. The ages of our subjects, including 10 men and 10 women, ranged from 20 to 65 years. In view of the small number of patients and the difficulties imposed by the acutely psychotic nature of our material, no attempt was made to differentiate our observations on the basis of age, sex or diagnosis. While an attempt was made to subject all our patients to both preoperative and postoperative tests, lack of cooperation, mutism and negativism frequently made preoperative records impossible to obtain. In view of the fact that our subjects were selected for operation on the basis of the symptoms, rather than of the diagnosis, a comparable control group was not available. However, the continuing nature of our study made it possible to use each patient as his own control. Thus, comparisons became possible between the various members of our experimental series, as well as between the preoperative and repeated postoperative records of each patient.

PSYCHOMOTOR PATTERNS

Our first efforts in the measurement of possible alterations in motor function were directed toward an analysis of polygraphic recordings, the technic introduced by Luria [6] in his psychoneurologic studies of behavioral dynamics being utilized. Early in our work we had hoped to study variations in neurodynamic age levels as suggested by Luria. It became evident, however, that changes in motor patterns were neither qualitatively nor quantitatively of a nature to allow analysis on this basis. The problem then became less structured and resolved itself into an effort to determine the general nature of the changes which took place in motor integration and the degree to which these changes, when present, correlated with variations in the clinical picture. Our patients were required to place the fingers of each hand in a metal receptor situated on top of an air pressure well. Voluntary and involuntary pressure of the fingers was transmitted, by means of air tube connections, to the pens of a polygraph, which recorded the movement on a moving tape. The polygraph contained a chronographic pen and an electrically activated stimulus marker, in addition to the pens recording movements of the right and the left-hand. Each of our subjects, when sufficiently cooperative to follow instructions, was required to perform a series of four operations of graduated complexity in the preoperative period and, again, during the postoperative course. In operation 1 the subject was required to press rhythmically on the receptor with the fingers of the preferred hand, while the other hand remained passive. The subject was permitted to select his own speed of rhythm. In operation 2 the subject was required to press rhythmically with the preferred hand as slowly as possible. In operation 3 the subject was required to

5. Goldstein, K.: The Organism, New York, American Book Company, 1939.
6. Luria, A. R.: The Nature of Human Conflict, New York, Liveright Publishing Corporation, 1932.

respond to a buzzer signal at regular intervals with the fingers of the preferred hand, while in operation 4 the subject was required to respond at irregular intervals. In each of these operations the subject was instructed to keep the nonpreferred hand immobile in the receptor.

In operation 1, in which the patient was required to press rhythmically with the fingers of the preferred hand, we found that the frequency range of rhythm tended to be greater for the preoperative patients than for normal subjects of comparable age and sex. The frequency ranged all the way from rapid, quick pressure to slow movements of a more deliberate kind. Another characteristic of our series of operative patients was the tendency to irregularity of rhythm and, in some cases, chaotic response. In general, the preoperative behavior, as one might expect, was characteristic of psychotic persons as a group. Operation 2, in which the subject was required to establish as slow a rhythm as possible, similarly reflected many psychotic trends. Our preoperative patients were unable to maintain a slow rhythm for more than a very short period. The result usually was a reversion to the faster natural rhythm established during operation 1, to a chaotic pattern or to a series of explosive reactions ending in complete block.

When our patients were required to respond to an auditory stimulus presented at regular intervals (operation 3), we observed that the ability to respond in a regular manner was much less than the ability observed in normal subjects. Our patients frequently established rhythms quite independently of the presented stimulus. One subject continued, at regular intervals, to respond with a pressure of the preferred hand when the stimulus was no longer presented. Other patients showed a pronounced trend toward extra signalizing. After the response to the presented stimulus the patient would make three or four attenuated responses, as if there was an overflow of energy. This overflow of energy, or lack of inhibitory control, was particularly evident in the synkinetic phenomena observed in this phase of our investigation. Synkinesis refers to the involuntary movement in one part of the body at the moment a voluntary movement takes place in another part. In our observations on this phenomenon, we noted both contralateral synkinesis and imitative ipsilateral synkinesis. In the latter the leg on the preferred side reproduced the movements of the preferred hand. The problem of synkinesis has been discussed at some length by Alajouanine and Thurel.[7] Synkinetic reactions were most extreme in operation 4, in which the subjects were required to respond to an irregularly presented auditory stimulus. Coupled with synkinesis, chaotic responses and extra signalizing, we found a prevalence of long anticipatory reactions. These preresponses were frequently so intense that the stimulus itself was overlooked. The reactions were made up of typical psychotic and psychoneurotic components. In view of the fact that our subjects were hospitalized for mental disease, these responses were to be expected and served to confirm our impression of the severity of the conditions with which we were dealing. After operation changes were observed in line with those already described in my study of abstract and categoric behavior[8] and neurolinguistic and neurosemantic tendencies.[9] When postoperative clinical improvement occurred, there were definite alterations in motor organization in the direction of more stable and symmetric responses. The frequency range of rhythm contracted; there tended to be less chaotic and irregular responses; extra

7. Alajouanine, T., and Thurel, R.: The Synkinesias, Encéphale **31**:97, 1936.
8. Kisker, G. W.: Abstract and Categorical Behavior Following Therapeutic Brain Surgery, Psychosom. Med., to be published.
9. Kisker, G. W.: Language-Structure and Meaning-Relationships Accompanying Artificial Destruction of Brain Tissue, to be published.

signalizing and anticipatory responses were diminished, and there was a decrease in synkinesis and blocking. In the clinically unimproved patients two divergent trends were observed. In one group no postoperative changes were observed, while in another there were certain changes in the direction of better motor organization, resembling those seen in our clinically improved patients. It was felt that this group had in some manner profited by the lobotomy, but that conditions were such that overt improvement was not possible. In any event, in not a single patient was the motor organization worse after operation than before.

VISUAL-MOTOR PATTERNS

Our second approach to the problem of perceptual-motor integration was patterned after the work of Wertheimer, Koffka, Kohler and other gestalt-oriented psychologists. The gestalt school of thought maintains that the structuralization of a configuration is dependent on the dynamic interplay of the sensory processes and the stimulus. These two factors, the internal and the external organizing forces, form a dynamic continuum by means of which primitive perception is established. The law of field genesis, with its emphasis on symmetry, stability and simplicity, incorporates such important dynamic factors as closure, proximity, pregnancy, goodness and the figure-ground relationship. Recent work has shown that the first changes in children, as well as those in mentally deficient persons and in certain patients with mental disorders, constitute a primitive motor pattern, which becomes defined with increased maturity or with clinical improvement or recovery. As early as 1932, Bender [10] studied the visual-motor patterns produced by mentally defective and schizophrenic persons and later [11] analyzed disturbances of gestalt function in the copied drawings of patients with organic diseases of the brain associated with sensory aphasias. More recently she [12] presented material related to similar functions in patients with dementia paralytica, alchoholic psychoses, traumatic psychoses and acute confusional states. Schilder [13] made similar studies of visual-motor gestalt productions after head trauma. In the acute confusional stage following the trauma there appeared to be a reversion to primitive features accompanied by disorientation wth respect to figure-ground relations. After the acute confusional period, there may or may not be impairment of function, as evidenced in reproduced drawings. In a few cases of severe trauma Korsakoff features were observed. These were characterized by approximately correct figure-ground orientation, but primitive reversions and interference with reproduction of parts of the figure appeared. Schilder expressed the belief that these features were due to confabulatory tendencies and pathologic motor impulses. Bender, Curran and Schilder [14] required a series of patients with the Korsakoff syndrome to draw repeatedly a gestalt figure. It was found not only that patterns changed their orientation but that figure-ground relationships became completely reorganized. Some of the changes in configuration were described in the following terms :

10. Bender, L.: Principles of Gestalt in Copied Form in Mental Defective and Schizophrenic Persons, Arch. Neurol. & Psychiat. **27**: 661 (March) 1932.

11. Bender, L.: Disturbance in Visuomotor Gestalt Function in Organic Brain Disease Associated with Sensory Aphasia, Arch. Neurol. & Psychiat. **30**:514 (Sept.) 1933.

12. Bender, L.: Gestalt Function in Visual Motor Patterns in Organic Disease of the Brain, Including Dementia Paralytica, Alcoholic Psychoses, Traumatic Psychoses and Acute Confusional States, Arch. Neurol. & Psychiat. **33**:300 (Feb.) 1935.

13. Schilder, P.: Psychic Disturbances After Head Injuries, Am. J. Psychiat. **91**:155, 1934.

14. Bender, L.; Curran, F. J., and Schilder, P.: Organization of Memory Traces in the Korsakoff Syndrome, Arch. Neurol. & Psychiat. **39**:482 (March) 1938.

The tendency to curves instead of angles may come into appearance. Figures may be contracted or expanded and elongated, especially in the horizontal plane. . . . The tendency to closure may become increasingly obvious. Adjoining configurations may be completely separated from each other. These changes take place in perceptive as well as in memory patterns and represent reversion to a primitive type of organization in the perceptive field.

In Schilder's [15] study of perceptual-motor patterns during metrazol shock therapy, a number of interesting observations were made which we suspected might in some way be applicable to the postoperative confusional period. I have already suggested that in our series of cases this confusion, described by Freeman and Watts and others who have recently interested themselves in the problem of lobotomy, was not verified as being a typical symptom. It is true that some confusion did follow several of the operations, but neither frequently enough nor to such degree that we felt it was a symptom of major prognostic, or other, importance.

The procedure used in our study of perceptual-motor processes, limited almost entirely to the visual field, was relatively simple and straightforward. A series of eight cards, each containing modified Wertheimer patterns of varying degrees of complexity, were presented, one at a time, to the subject, who was required to study the pattern for an unlimited time and was then asked to reproduce the design from memory. Twenty-four hours later another reproduction was called for in the absence of any cues. The problem of whether the patient should be allowed to copy the design or to reproduce it from memory is an interesting one. In discussing Bender's study of gestalt function in the visual-motor patterns of patients with organic disease of the brain, Wertheimer stated that the method of copying a drawing which is continuously in view is questionable because there is a tendency toward disintegration of figural patterns and it is not known what is conditioned by the tendencies of the visual field and what is conditioned by motor abilities. In the light of this criticism and in consideration of the nature of the problem, it was decided that the greater emphasis should be placed on the reproduction of patterns in the absence of the original. Such a procedure permitted us, to a limited extent, to study the influence of lobotomy on the memory trace system of our patients. In several instances in which it was impossible to obtain delayed reproduction, even after the briefest interval, the subject was allowed to copy the designs directly from the cards.

In our series of patients, the reproduction of designs and the subsequent analysis of the reproduced material, with particular emphasis on gestalt principles, failed to reveal widespread impairment of the so-called gestalt function. It is quite true that various forms of reproduction were encountered, but it was felt that the greater part of this variation was to be explained in terms not of direct intrusion as a result of the interruption of the frontal fibers but of secondary, supporting factors.

MOTOR COORDINATION

In a further effort to sample motor behavior in as many areas as possible, we subjected each of our patients to a periodic analysis of the general fields of speech functions and gait and the more limited fields of praxis and gnosis. As far as could be determined, the motor components of speech and gait remained unchanged as a result of bilateral prefrontal lobotomy. In a few patients apraxis and agnosic phenomena were observed, and it is to these atypical signs that the present discussion is directed. In determinations of right-left orientation, we

15. Schilder, P.: Notes on the Psychology of Metrazol Treatment of Schizophrenia, J. Nerv. & Ment. Dis. 89:133, 1939.

observed a patient who as late as the fifth postoperative week had difficulty in this area. I have discussed elsewhere the more widespread disturbances of spatial, temporal and personal disorientation,[1b] and I shall not go into detail at this time. While disorientation of necessity resolves into a motor dysfunction, I am thinking here of these disturbances in a more restricted sense. Such disturbances, never pronounced, were suggested in our study of praxis, optic-finger praxis and constructive praxis. In tests of the first two functions our patients were required to handle objects and to imitate finger gestures. Disability in these areas was infrequent and when present was seldom serious. More decided disturbances were observed in the tests of constructive praxis, in which the patients' were required to make drawings, to work with wooden mosaics and blocks and to reproduce designs. The results in our study of gnosis were almost entirely negative. Our work in this area included tests of stereognosis, finger gnosis and autotopagnosis. While none of the typical neurologic syndromes were revealed in this area, transient autotopagnosic phenomena were seen from time to time in the early postoperative course. With respect to the general problem of motor phenomena, particularly the areas of praxis and gnosis, it must be said that frontal lobotomy is not an important factor. The disturbances in these functions are to be interpreted in terms of the psychotic manifestations rather than of neurologic dynamics.

SUMMARY AND CONCLUSIONS

The experimental work carried out on perceptual-motor processes seems to indicate that in this particular series of cases bilateral prefrontal lobotomy did not have an appreciable effect on the elementary motor integrative functions. In none of the patients was postoperative disturbance noted when there had been no preoperative disturbance. This situation held for all of the tests used in the evaluation of motor processes. It is true, of course, that there were instances in which preoperative disturbance disappeared after the lobotomy. We attribute this increased motor efficiency to a reflection of increased total adjustment on the segmental, or partial, patterns of behavior. We do not believe that there had been reorganization on a primarily motor level or that motor integration in the brain had been disturbed as a result of interference with intrafrontal connections or frontothalmopontile connections. While it must be admitted that animal studies have shown a definite relation between the frontal poles and motor function, the work with human material has not demonstrated the extreme motor dysfunction noted in lobectomized animals. This seeming contradiction, we believe, is to be explained in terms of differences in the cytoarchitectonic organization of the human brain and that of the lower animals. We have found, in our work with lobotomized patients, that while automatic acts, restlessness, synkinesis, gestalt dysfunction, apraxis and agnosis are sometimes observed both before and after operation, and that while these signs occasionally disappear after the neurosurgical procedure, the essential factor is the destruction of psychotic attitudes rather than altered neurodynamic organization. Thus, while the operative group showed both pre-operative and postoperative motor irregularities, and while the postoperative irregularities of patients who showed improvement were less pronounced than those displayed in the preoperative period, the pattern of motor dysfunction approximated that of psychotic patients in general. As clinical improvement became apparent, improved motor integration occurred, although there was no evidence of motor disturbances related specifically to frontal lobotomy.

6321 Delphos Avenue.

USE OF INSULIN AS SEDATION THERAPY

CONTROL OF BASIC ANXIETY IN THE PSYCHOSES

THOMAS A. C. RENNIE, M.D.

NEW YORK

The use of insulin for the production of coma in the therapy of the psychoses has not fulfilled the expectations of a few years ago. A careful review of the literature [1] leaves no doubt that it has a definite place in the proper hands and in the management of the total problem. Most observers agree that its greatest advantage lies in the treatment of schizophrenia. Electric shock seems likely to replace insulin in treatment of all the affective conditions because of its better results and easier technic.

The effectiveness of insulin in subcoma doses has received little attention. In this paper are described the results obtained in treatment of various psychopathologic conditions with a technic which stops short of the production of coma. Twenty-eight patients have thus far received this modified type of insulin therapy, with the production of somnolence and clouded consciousness, the treatment stopping just short of loss of consciousness and stupor phenomena (occasionally clonic twitchings and primitive movements occur). The neurologic effect has been thought to be a suppression of cortical and cerebellar activity, with possible release of activity associated with the basal ganglia and hypothalamus. The method offered complete safety and had none of the hazards of the coma or shock procedure.

METHOD

Each patient to be treated had a complete physical examination and a roentgenographic study of the chest. Complete studies were made on the blood, including determinations of the sugar content, cell count, specific gravity, nonprotein nitrogen level and insulin tolerance. Treatment was given six days a week, the dose starting with 10 units of insulin and being increased 10 units daily until the amount was reached which produced deep sleep from which the patient could still be aroused with strong stimuli. Usually 50 to 90 units sufficed. Occasionally light coma occurred, but the patient was deliberately kept from proceeding into deep coma. The patient's verbal productions under the effect of insulin were recorded and utilized for intensive psychotherapy during treatment.

RESULTS

The investigation was begun as a study of methods of controlling excitement. Soon it became apparent that with insulin dramatic relief of anxiety could be achieved in various kinds of excitement: schizophrenic, depressive and suicidal overactivities, and panic states—wherever, indeed, basic anxiety prevailed. It is the specific effect of insulin in the relief of anxiety that will particularly be described. The first patient selected for treatment showed a striking response in the sudden disappearance of anxiety and suicidal drive.

CASE 1.—A lawyer aged 24, unmarried, was in a serious depression. Three days after his admission to the hospital, on Sept. 9, 1941, acute suicidal excitement developed, and he made constant impulsive attempts to injure his head, choke himself, drown himself, pull out his tongue and rip off his genitals. He came of a family heavily loaded with manic-depressive psychoses.

His father had a circular manic-depressive illness, for which repeated hospitalization was required. A paternal uncle had recurrent depressive episodes. A paternal aunt was hospitalized for ten years with a circular manic-depressive psychosis. A maternal uncle was alcoholic. The patient's sister had a depression lasting three months. His younger brother had a serious depression, for which he was hospitalized at the time this patient was admitted.

The patient's own illness began insidiously in February 1941. In September, just before his approaching marriage, he had an acute anxiety attack, became profoundly depressed and self depreciatory, made serious suicidal attempts and had to be admitted to this clinic five days later. The persistent suicidal attempts constituted an acute emergency; two special nurses were assigned to prevent his repeated self-destructive acts. Anxiety was evident in the rapid pulse and the fasting sugar content of the blood of 111 mg. per hundred cubic centimeters. For eight days he was given 0.4 Gm. of sodium amytal every six hours and was quieter. On cessation of medication he immediately resumed his self-destructive attempts. Insulin therapy was started with injection of 20 units, the dose being increased 10 units daily until the sixth day, after which his status was maintained on 50 units. In all, thirty-one treatments were given. At the end of six days, his excitement entirely disappeared; his suicidal attempts subsided, and he continued to improve steadily. During insulin treatment he was usually euphoric, frequently singing "I'm a sinner." Sleep and weight rapidly improved. He was soon able to discuss his suicidal urges, his underlying anxiety toward his impending marriage and his fears that his genitalia would be too small. Active psychotherapy was thus made possible. He was discharged from the hospital four months later, almost recovered. A month later he had recovered entirely and had excellent insight into the motivations of his aggressive, self-destructive behavior.

In this case, the drop in pulse rate, the diminution of anxiety, the change from depression to euphoria during insulin treatment and the ease in talking, all pointed to a striking alteration of affective tone in the patient. A study of this patient after recovery forced an appreciation of the large role that anxiety played in the perpetuation of the psychotic process and the remarkable improvement that could be expected when the anxiety was relieved. In the next case, one of homosexual panic with an acute excitement, an equally dramatic improvement was obtained through the cessation of anxiety.

CASE 2.—An unmarried man aged 23 entered the hospital on Feb. 22, 1942 in an acute schizophrenic excitement, with features of homosexual panic. He showed severe anxiety and fear, flushing, perspiration, rapid pulse and erotic gestures. Extreme anxiety was indicated by the high pulse rate, the elevated white cell count of 13,750, poor sleep and loss of weight. Administration of sodium amytal had no effect. He showed marked distractibility and flight of ideas, expectorated on the floor, was incontinent of urine, manifested decided aversion to male nurses, was mischievous and unpredictable in behavior and became assaultive to the nurses. After two and one-half months without improvement in his excited behavior, insulin therapy was begun, the maximum dose reached being 85 units. Thirty-four treatments in all were given, each dose being usually 75 units. Almost immediately his behavior improved. After five weeks the excitement was terminated. Insulin therapy enabled the patient to discuss his sexual preoccupations, family problems and other difficulties. Fear and anxiety disappeared. Improvement continued steadily until his complete recovery.

It soon became evident that insulin therapy affected anxiety in all varieties of the schizophrenic disorder. The effect was well demonstrated in the following case of acute catatonic stupor.

CASE 3.—A student nurse aged 20 was admitted to the hospital on Dec. 18, 1942. Her illness began one week prior to admission, during her first week of training, when she was homesick and unable to make friends, feared she had failed a test and suffered from the delusion that she was involved in an abortion. She complained of feelings of unreality and difficulty in concentration and in expressing herself. Within three days she became increasingly apprehensive and anxious and spoke of disturbing voices. She was preoccupied with thoughts of dying. During the first several days in the hospital she was extremely fearful, screamed, thought she was to be killed and heard her mother's and father's voices. She then became mute and resistive and passed into a typical catatonic stupor, with rigidity, incontinence and retention of saliva. Anxiety was indicated by poor sleep, a rapid pulse with a rate of 130, and elevation of the blood sugar (125 mg. per hundred cubic centimeters). With *intravenous*

administration of sodium amytal she showed little relaxation. Insulin therapy was started ten days after admission and was continued for fifty treatments, with a maximum dose of 65 units. Within three weeks, her stupor was terminated; the anxiety had disappeared, and she became more accessible to psychotherapy. Six months later she was discharged as recovered, having discussed at great length her personality makeup and difficulties.

Through the rapid alleviation of anxiety, with the consequent improvement in the whole disorder, these patients became accessible to intensive psychotherapy. Yet even when psychotherapy was not possible, the mere alleviation of anxiety brought about symptomatic improvement. This was illustrated in another type of schizophrenic disorder.

Case 4.—A single woman aged 24, in a state of hebephrenic scattering, had an insidious onset of her illness eight months prior to admission, on Jan. 9, 1942, when she suddenly confessed to her mother having had sexual relations. She continued at work but complained of abdominal pain and fatigue, was suspicious of her mother and accused her of having an affair with her adopted son. The patient spoke of her employer's making advances to her and alternated between depression and inappropriate giggling. She seemed preoccupied with war and sexual topics. She grew more restless, wandered about at night and finally became incoherent. Her course in the hospital was marked by three well defined episodes of excitement.

Five days after admission she became increasingly apprehensive, refused meals, showed fear and anxiety and made references to her losing her soul, going to hell and being dead. The period of sleep ranged from four to six and a half hours. On the third day in the hospital the pulse rate increased suddenly to 110 a minute. She became excited and panicky, disorganized in her activity and incoherent in speech. With administration of barbital, 0.15 Gm. three times a day, and sodium amytal, 0.4 Gm. at night, this excitement subsided rapidly, and her pulse rate dropped. On January 26, while she was still under treatment with sedatives, her pulse rate began to rise. On January 30 use of barbital was discontinued, in preparation for insulin treatment. In the next three days her pulse rate rose to 130. She became excited and panicky, disorganized in her activity and incoherent in her speech. She was hallucinated, appeared much frightened and shouted continuously to drown out the hallucinatory voices. In spite of the sodium amytal, she did not sleep at all for two nights. The patient was in an acute excitement when insulin therapy was begun, on February 4, with injection of 25 units. The dosage was increased gradually until 85 units was being utilized. On the second day of insulin therapy sleep began to improve. At the end of one week of the therapy, when the dose had reached 55 units, the most severe fear, tension and anxiety had largely disappeared. She continued to improve rapidly, was better oriented and more in contact with her environment and seemed more cooperative and sociable. In spite of her improved appearance and behavior, she was not able to talk coherently with her physician but remained silly. She talked with other patients in a superficial manner but was able to visit on a floor for patients in a more advanced stage of convalescence. In all, twenty-one insulin treatments were given. On February 18 and 27 and March 8 an untoward convulsion occurred early in the morning, within one hour after injection of insulin in doses of 85, 100 and 80 units respectively. For this reason, and because of her improvement, insulin therapy was stopped on March 8. Sleep at this time was adequate with administration of 0.2 Gm. of sodium amytal at night. Immediately on cessation of insulin treatment tension increased. Within a week she asked to be moved back to the floor for disturbed patients, where she spent an entire night praying in an agitated manner. Once more anxiety and fear became prominent. On March 15, treatment with 50 units of insulin was again started, preceded by hypodermic injection of 0.13 Gm. of phenobarbital. Immediately her behavior again began to improve. In four days her spiking pulse leveled off; sleep definitely improved; tension and anxiety diminished, and she was able to resume visiting on a floor for semiconvalescent patients. She went into coma with a dose of 55 units and hence her status was maintained on 40 units. After fifteen insulin treatments, without occurrence of convulsions, she returned to socially adequate behavior, but with notable vagueness in conversation. Her weight steadily increased, and the acne with which she was afflicted was much better. She maintained this improvement for four weeks. Again her behavior became scattered and hebephrenic, and she was transferred to another hospital.

In this patient, insulin achieved better results than could be obtained with drug sedation. Two episodes of excitement with fear, tension and anxiety soon quieted down under treatment with insulin, and she was left superficially improved but with many evidences of personality disorganization, as shown by her flat affect.

inappropriate responses, changes of mood and vague expressions of delusional ideas of control. This case illustrated that insulin cannot be expected to modify a fundamental schizophrenic process. Its real effectiveness here lay in the control of the excitement, and it constituted an effective adjunct to the total psychiatric therapy.

The effectiveness of this form of insulin therapy in reducing anxiety was not limited alone to the schizophrenic process. The same striking result was shown in a youth aged 20 with severe manic excitement and recognizable underlying anxiety.

CASE 5.—A Jewish student aged 20, single, entered the hospital on Feb. 21, 1943 after two weeks of increasing restlessness, overtalkativeness, elation, sleeplessness, push of talk and humming, this excitement terminating one day previous to admission in confused, disoriented behavior. On admission he was extremely tense, with considerable anxiety underlying his elation. Although anxiety was manifested in an extremely rapid pulse, the sugar content of the blood was not elevated, being 93 mg. per hundred cubic centimeters. He spoke freely of his auditory hallucinations, of the voices directing his activities, of his preoccupations concerning his fear of induction into the Army and of his sexual life and his bodily functions. Three weeks later there developed more intense excitement of an erotic nature; he exhibited aggressive and assaultive behavior and showed a definite paranoid state, with delusions suggestive of schizophrenic features. His pulse and blood pressure became elevated, and his hypochondriacal concern became more and more severe, centering around anxiety concerning his heart. At the height of his excitement insulin therapy was begun. In all, fifty treatments were given, the maximum dose being 80 units. Within six days the excitement had begun to subside, and the patient was able to gain rather remarkable insight. In psychotherapeutic sessions he was able to discuss at length his concern about his draft status, his sexual orientation, his resentment toward his parents, his need for emancipation from home and his plans for the future.

In several of the patients hallucinatory experiences rapidly disappeared as the anxiety was relieved. What happens in the psychopathologic processes of such patients under insulin treatment is of great interest and may offer an opportunity to obtain insight into the dynamics productive of anxiety.

CASE 6.—In an 18 year old Jewish youth an acute psychosis developed with schizophrenia, one week after induction into the Army. He entered the service willingly, but with fear and much bravado, was uneasy and feared he was going to be shipped abroad. Five days after induction, while on the train en route to another camp, he became acutely disturbed and combative, appeared disoriented, saw snakes and blood and was suspicious of some one's cutting off his legs. On admission to this hospital, one month later, he appeared restless, overactive, tense and suspicious and obviously was hearing voices. With barbital sedation during the first week he became quieter, but was seclusive and negativistic and plugged his ears to shut out the voices. With intravenous administration of sodium amytal, he easily discussed his main preoccupations, saying that he was convinced he was still in the Army and that he was discriminated against for being a Jew. He had delusions that his parents had been killed, his legs cut off and his blood drawn from him. Two weeks later insulin therapy was begun, and in seven days, when the dose had reached 65 units, the voices had entirely disappeared. The patient was free of delusions; his paranoid suspicions had cleared, and he remained pleasant, cooperative and friendly throughout the rest of the day. His improvement continued. Some two weeks later he was well enough to be visiting on the convalescent floor. Clearly, the rapid improvement was due to the immediate relief of his underlying anxiety.

In the manic patient (case 5) anxiety could be witnessed in its actual evolution. Basically, the patient feared induction into the Army. In his manic state he exhibited sexual upheaval, with erotic talk and behavior toward the nurses. He discussed freely how he wanted to avoid the war and how he was concerned with fear for his sister's reputation. Throughout this time, with ventilation of these dynamic factors, his excitement was diminishing. Ten days later he began a discussion of the Jewish problem, relating it to his rejection of his parents and the position in life which they offered him. The next day he discussed at length his

resentment of his uncle, a physician, who, during a physical examination several years previously, had frightened him about his cardiac status. On the third day a necessary physical examination stirred up considerable anxiety in him over this condition. He refused any further examinations. With this sudden reactivation of his anxiety, sexual factors again came into the foreground. He was erotically stirred by a new nurse on the floor. He began talking of his sexual preoccupations under considerable pressure. He told one of the male nurses of his impotence with a prostitute several years before. After this his excitement greatly increased, and his ideas were increasingly paranoid and fearful, he became openly assaultive and struck at male nurses, identifying them with the man whom he thought had seduced his sister. Auditory hallucinations developed. At this point insulin therapy was started, with rapid subsidence of the excitement and disappearance of the delusional and hallucinatory experiences. In this case increased anxiety kept alive the dynamic sexual factors leading to paranoid psychotic manifestations; with relief of the anxiety through insulin therapy, the dynamic factors subsided, and the psychotic elaborations disappeared. The following case illustrates severe tension with auditory hallucinations and their disappearance under the influence of insulin, which relieved the tension.

CASE 7.—A woman aged 26, with schizophrenia of one year's duration, had responded once previously to treatment with insulin and metrazol. On admission to this hospital, she showed a well advanced disorganized, scattered state. She complained a great deal of tension, which was manifested in her rapid pulse and fragmented sleep. After her first menstrual period she became tense, agitated, fearful and incoherent. Her tension mounted. She expressed fear of insanity, and in this setting of growing anxiety auditory hallucinations appeared. With insulin therapy her tension rapidly subsided. She spoke of "the falling away of my symptoms," meaning her auditory hallucinations. In her behavior she became much less vague, and conversation was better organized. Throughout the remainder of the period of treatment with insulin she remained free from delusions and hallucinations.

In this patient a dramatic relief of underlying tension resulted in complete disappearance of the active psychotic process, even though at no time was she able to profit from any intensive psychotherapeutic investigation of her problem.

COMMENT

Scrutiny of the results in these cases of depressive, manic and schizophrenic reactions reveals that the psychopathologic state was strongly influenced by the presence of basic anxiety and that in each case the modification effected seemed to lie in the specific disappearance of the dynamic anxiety.

In order to understand the results achieved, a review of the various concepts offered to explain the action of the so-called shock therapies was undertaken. While insulin, metrazol and electric shock treatments are all grouped together as shock therapies, their action on the human subject is quite different. The manner in which these procedures effect improvement is not known. Many theories have been advanced. Berze [2] expressed the opinion that the mechanism was like that in certain old psychiatric methods used to scare patients out of their delusions by making them fight for their existence. Boss [3] saw in it the appeal to the instinct to self preservation through the fear of death, and Jelliffe [4] viewed

2. Berze, J.: Die Insulin-Chok-Behandlung der Schizophrenie, Wien. med. Wchnschr. **49**:1365-1369, 1933.

3. Boss, M.: Die Grundprinzipien der Schizophreniebehandlung im historischen Rückblick, Ztschr. f. d. ges. Neurol. u. Psychiat. **157**:358-392, 1937.

4. Jelliffe, S. E., in discussion on Wortis, J.: Hypoglycemia Treatment of the Psychoses, Arch. Neurol. & Psychiat. **38**:191 (July) 1937.

hypoglycemia essentially as a death threat. Bychowski [5] postulated a partial destruction of the pathologic ego, and Glueck,[6] a strengthening of the forces of control, whereas Schilder [7] stressed the joy of rebirth after awakening from coma. He commented that after the shock most patients felt relaxed, free from anxieties and more ready to trust people about them. Weigert [8] emphasized the possibility of establishment of transferences in the period immediately after shock. Piers [9] offered a psychoanalytic interpretation in the guiltless fulfilment of immense oral craving. Shapiro and Freeman [10] and Friedman [11] saw definite therapeutic value in the production of a period of confusion and amnesia. These authors overlooked the fact that although the amnesia produced may be involved in the rapid transformation, it is not likely to be the whole explanation, since the patient often maintains his improved status even though his memory returns.

From the study of the present series of patients, it seems that a different and specific mechanism involved in the action of insulin can be defined. As long ago as 1912, Bleuler [12] pointed out that affects and feelings can be absorbed into delusional formation. He stated that in cases of schizophrenia affective experiences were transformed into hallucinations and delusions, although the original affect could not be demonstrated or had become rudimentary. It seems possible that anxiety, like other affects, may lie behind delusional developments, only to be ultimately incorporated into the delusional system so that its role is no longer clearly seen. The results with patients 6 and 7 indicate that anxiety tends to keep dynamic factors alive and that relief of the anxiety permits them to subside. Owing to the influence of Freud, it has long been thought that sexual frustration causes anxiety. On the other hand, Féré [13] pointed out that anxiety itself may cause sexual excitement. Sakel, in 1933, was the first to demonstrate that insulin could be successfully employed in diminishing the unpleasant anxiety symptoms related to withdrawal from morphine addiction. The results would indicate that Bleuler's formulation of 1912 deserves serious reconsideration now.

In a study of this entire series, including patients with depressive and panic reactions, as well as schizophrenic conditions, possible indications for the effectiveness of insulin therapy seem to lie in the specific control of anxiety and fear. Instead of anxiety's being considered as a discrete phenomenon, or entity, the extent to which it may permeate all psychopathologic reactions should be evaluated. Thus it may be a leading factor in an empty, scattered hebephrenic state, in catatonic stuporous withdrawal, in panics, in all kinds of excitement, even in elated manic states, in which often the patient in retrospect describes well the unhappiness and

5. Bychowski, G.: Psychoanalyse im hypoglykämischen Zustand, Internat. Ztschr. f. Psychoanal. **23**:540-547, 1937.

6. Glueck, B.: The Effect of Hypoglycemic Therapy on the Psychotic Process, Am. J. Psychiat. **94**:171-174, 1937.

7. Schilder, P.: Notes on Psychology of Metrazol Treatment of Schizophrenia, J. Nerv. & Ment. Dis. **89**:133-144, 1939.

8. Weigert, E. V.: Psychoanalytic Notes on Sleep and Convulsion Treatment in Functional Psychoses, Psychiatry **3**:189-209, 1940.

9. Piers, G : Prognostic Observations in Insulin Treatment of Schizophrenia, Elgin State Hosp. Papers **4**:34-45, 1941.

10. Shapiro, H. D., and Freeman, W.: Shock Therapy (Insulin and Metrazol) in Neuroses, M. Ann. District of Columbia **8**:65-72, 1939.

11. Friedman, E.: Irritative Therapy of Schizophrenia, New York State J. Med. **37**:1813-1821, 1937.

12. Bleuler, E.: Affectivity, Suggestibility, Paranoia, translated by C. Ricksher, State Hosp. Bull. **4**:481-601, 1912.

13. Féré, C.: The Sexual Instinct: Its Evolution and Dissolution, translated by H. Blanchamp, London, London University Press, 1900.

prevailing anxiety behind the expression of elation. That anxiety may occur in all varieties of psychotic reactions is evident from the case histories previously cited. Clinical categories of terms too often becloud this fact by the assumption that mania is a state of pure elation, depression one of pure sadness and schizophrenia one of split affect. A psychosis is a method of reacting to personality or life factors; dynamically, it must be recognized that conflict or anxiety lies behind all such developments. This may explain the failure of the psychiatrist to define any bio-chemical factors specific to schizophrenia. He has been looking for factors specific to a disease entity; what he finds are factors that are variable from case to case and may be far more related to the anxiety component than to a schizophrenic entity as such. In schizophrenia, attempts to define a specific factor responsible for the condition have led to varied and contradictory claims. Among the multiple physical alterations sometimes actually claimed as etiologic factors are: fever on admission, various cutaneous manifestations, erratic and depressed pulse rate, low blood pressure, diminished oxygen consumption, vascular hypoplasia, small heart, dropped heart, slow circulation time, low circulating volume of blood, cyanosis, dermatographia, vasomotor disturbances and gastrointestinal irregularities. Reaction to pilocarpine and epinephrine and changes in vasomotor tonus have been thought to point to an unstable autonomic nervous system. The chemical observations on the body fluids and the blood point to leukocytosis; a normal, or perhaps sustained, blood sugar metabolism; low fatty acid and cholesterol contents of the blood, and a normal calcium content. The neurologic data point to low heat production and abnormal heat regulation and to diminished or poorly active respiratory regulation. Definition of the endocrine status is poor, hinging on implication only of changes in the anatomy or the function of the sex glands, thyroid, parathyroid and pituitary. Theoretic consideration has been offered for the involvement of the hypothalamus, the diencephalon and the posterior lobe of the pituitary. Most of these somatic changes can be better explained as physiologic expressions of basic anxiety—hence their variability from case to case.

Relief of anxiety would seem, then, to be a constructive approach to any of the psychotic conditions. The patient's statements frequently support the fact that insulin alleviates anxiety. A catatonic, stuporous girl said: "Maybe it was the relaxing that helped me. I have been frightened for months, and I was finally able to tell the doctor about it." A patient in a schizophrenic excitement said: "For the time being it relaxes me. It takes me away from myself." A patient in a hallucinated, disorganized schizophrenic state said: "The particular insulin I don't like so well. It makes you better. The insulin stopped the voices, the noises. It calmed something down." Another hebephrenic patient replied: "It relaxes me and makes me more at ease." A recent patient in whom a catatonic stupor was averted replied while under insulin treatment: "I feel more composed inside."

Aside from the patient's own statements, evidences of diminishing anxiety were frequently seen in a drop in pulse rate; a lowering of the sugar content and white cell count of the blood[14]; a fall in blood pressure; an increase in sleep, appetite and weight; disappearance of sweating, with improvement in the condition of the skin and occasional disappearance of unexplained mild fever.

The observations on patients 3, 4, 6 and 7 suggest that Bleuler's original consideration may be correct—that a strong affective experience, such as anxiety, can produce actual hallucinatory phenomena. In another patient (case 5) the observed

14. Milhorat, A. T.; Small, S. M., and Diethelm, O.: Leukocytosis During Various Emotional States, Arch. Neurol. & Psychiat. **47**:779-792 (May) 1942.

disappearance of delusional developments, with relief of the anxiety, again supports this thesis. While it is true that in some patients sedatives may appear to suppress an excitement, in most of the patients observed the sedation did not persist after withdrawal of the drug, while the effect of insulin was lasting. Catharsis seems an important part of the total effect. In several of the patients this was achieved briefly with intravenous administration of sodium amytal. The claim that a good response to sodium amytal foretells a good response to insulin cannot be supported. Eight of the patients received intravenous injections of sodium amytal. Six responded well and talked freely under the effect of the drug; yet 3 of these patients were among the 5 who responded poorly to insulin. Two showed only slight response; yet 1 of these (patient 3) responded well to insulin. One patient in catatonic stupor responded well to amytal and discussed his fears. With insulin the actual fear was reduced but no real ventilation was achieved. The response to intravenous injection of sodium amytal, therefore, seems not to be an absolute criterion of good response to insulin.

The attitude of the patients to the treatment varied considerably. A number of them were frightened by it, and several were openly antagonistic and could see no benefit from it, even though their condition had clearly improved. Two patients asked for the treatment. The remainder accepted the therapy without protest.

Whatever actual physiologic process occurs remains to be defined. The fall in the blood sugar is the most striking phenomenon to witness. Little is actually known about the manner in which hypoglycemia affects the human system. It is accepted that cerebral anoxemia occurs during hypoglycemia. Consumption by the brain of both dextrose and oxygen is notably reduced. Other studies have revealed an increase in the secretion of the parotid gland, an increase in free and combined acidity of the gastric juice, an increase in leukocytosis and a decrease in the nonurea nitrogen, amino acid, potassium and inorganic phosphorus contents of the blood.

It seems likely that these chemical constituents decrease because of the withdrawal of sugar from the blood stream, and presumably its deposition in the liver. These changes might be interpreted as a vagotonic response, although both the parasympathetic and the sympathetic nervous system may be involved.

CONCLUSIONS

In 28 patients who received this form of insulin therapy the results obtained were striking. Nineteen of the series showed marked clinical improvement, clearly justifying the method. Four others displayed some improvement. Only 5 of the group can be considered to have derived no benefit from the procedure. Of these 5, 3 represented depressive and 2 schizophrenic reactions. These patients for whom insulin therapy failed had strong catathymic reactions and rigid, unbending personalities, in which either the psychopathologic process seemed uninfluenced by anxiety or the anxiety was so fixed and absorbed into the delusional system that it could not be released. The 19 patients who showed improvement and the 4 patients who manifested slight improvement included persons with schizophrenic excitements, panic, catatonic stupors, hebephrenic dilapidation, suicidal depressions, depression with marked aversion (1) and manic excitement (1). The therapy proved a valuable method in aversion of stupors, interruption of frightening hallucinations and establishment of rapport. It permitted a marked degree of relaxation, released ability to discuss preoccupations easily and thereby provided the therapeutist a real opportunity to get closer to the patient and his inner needs. It

permitted catharsis in certain strained fear states. Sometimes even when the patient never discussed any fundamental dynamic material, it released inner tension and strikingly relieved anxiety and fear. In short, it provided the best available method of permitting the patient to utilize psychotherapy. In every case active psychotherapy was carried out hand in hand with the administration of insulin. The method is one which placed the physician in a particularly valuable role with his patient. It provided a bridge to active psychotherapy. No claim can be made that the therapy constitutes a cure for a disease entity. Any procedure which can so effectively reduce anxiety, fear and tension of necessity makes the management of the patient easier, reduces the need for chemical sedation, provides four or five hours during treatment of effective sedation in rest and permits the interruption of preoccupations, which otherwise are kept alive by the basic anxiety. With the cessation of anxiety one can prevent rut development and features of aversion and negativism and can achieve freedom from hallucinations and avoidance of many of the psychopathologic features considered characteristic of the schizophrenic patient, such as disorganization of thinking and behavior. The effects of insulin are more incisive and lasting than chemical sedation, which appears not to achieve any such profound alteration of the basic anxiety.

Insulin seems to be a good means of achieving effective sedation. If it works primarily by reduction of anxiety, it deserves a fuller study in treatment of the essential anxiety neuroses. Its use should be tried also in general hospitals for such conditions as postoperative excitements.

One can only hypothesize why a physiologic procedure such as insulin therapy should be effective. Some profound action on the central nervous system, presumably on autonomic centers, must be postulated.

SUMMARY

Administration of insulin in subcoma doses provides an effective method of sedation. Its specific action seems to be in alleviation of anxiety. With relief of anxiety, the psychotic manifestations sometimes rapidly disappear. The method is entirely safe and is far superior to that achieved by chemical sedation. Combined with active psychotherapy, it has proved of great value in the treatment of a series of difficult patients.

New York Hospital.

Case Reports

FAMILIAL MULTIPLE SCLEROSIS

Leo A. Spiegel, M.D.,* and Moses Keschner, M.D., New York

The paucity of recorded cases of familial multiple sclerosis verified by necropsy has prompted us to report 2 such cases which we observed at the Montefiore Hospital. Many authors doubt or deny the occurrence of familial multiple sclerosis. "Some of the cases referred to," said Bramwell,[1] "have undoubtedly belonged to the category of familial spastic paraplegias." Putnam [2] stated:

There are, to be sure, occasional instances in which two cases have occurred in the same family, but they are probably to be ascribed either to coincidence, or to confusion with hereditary ataxia which sometimes closely simulates multiple sclerosis.

The majority of the reported cases have been described only clinically, and in view of the protean character of the disease it seems inadvisable to accept such cases as evidence of proved familial multiple sclerosis. A few cases, however, have been reported with necropsy.

Kramer [3] reported the case of a woman aged 49 whose disease began with a feeling of heaviness in the lower extremities, occasional diplopia, loss of urinary control, difficulty in speech and impairment of skilled movements. Examination disclosed congenital bilateral dislocation of the hips, slight nystagmus, slight temporal pallor of the optic disks, spastic paraparesis with increased knee jerks and ankle clonus, and the presence of Babinski, Mendel-Bechterew and Rossolimo signs. The patient's condition improved, and on reexamination one year later only pallor of the disks and slight nystagmus were observed. Necropsy was not performed in this case, but examination of the spinal cord of the patient's sister, the clinical picture of whose illness was not given, revealed lesions typical of multiple sclerosis. Schob [4] reported the cases of a brother and sister, with necropsy in each. The age of onset of the disease in the brother was probably about 37 years. There was no record of a detailed neurologic examination other than the notation of hyperreflexia, a positive Romberg sign and ataxia. However, the presence of the last two signs was considered questionable because simulation was suspected. The sister probably became ill at about the age of 29 years. Examination showed spastic paraplegia, absence of abdominal reflexes, a bilateral Babinski sign, end point rotary nystagmus, intention tremor and atrophy of the temporal half of the optic disks. At the age of 24 years the question of hysteria had been raised. Necropsy disclosed typical lesions of multiple sclerosis in both the sister and the brother. Thomas [5] reported clinically cases of multiple sclerosis in a mother and a daughter. The latter's illness ran an acute course and probably was a form of so-called acute multiple sclerosis, or encephalomyelitis. Examination of the spinal cord of the daughter, as reported on later by Cournand,[6] revealed typical plaques of multiple sclerosis.

1. Bramwell, E.: Modern Medicine, Philadelphia, Lea & Febiger, 1910, vol. 7, p. 145.
2. Putnam, T. J.: Multiple Sclerosis and Encephalomyelitis, Bull. New York Acad. Med. 19:301, 1943.
3. Kramer: Demonstration aus dem Gebiete der Heredodegeneration, Zentralbl. f. d. ges. Neurol. u. Psychiat. 25:232, 1921.
4. Schob, F.: Ueber multiplen Sklerose bei Geschwistern, Ztschr. f. d. ges Neurol. u. Psychiat. 80:56, 1922.
5. Thomas, A.: Sclérose en plaques chez la mère et la fille, Rev. neurol. 2:714, 1929.
6. Cournand, A.: La sclérose en plaques aiguë, Thesis, Paris, Amédée Legrand. 1930.

Our cases were those of a brother and a sister, in both of whom the clinical picture conformed to the generally accepted symptomatology of multiple sclerosis, and in 1 case (that of the brother) the clinical diagnosis was verified histologically.

REPORT OF CASES

CASE 1.—S. F., a married woman aged 55, was admitted to the Montefiore Hospital on April 9, 1940, complaining of easy fatigability and progressive weakness of the lower extremities of seven years' duration. Three years before admission she began to have burning pains in the left leg and aching pains in the right leg. One year later urgency of urination appeared, and one year after that spontaneous flexion of the right lower limb occurred at the knee, which soon assumed a flexion deformity. At about the same time she experienced double vision on extreme lateral gaze. Three months before admission she became bedridden because of flexion of both legs at the knees.

Her past medical history was noncontributory. Her family history, she maintained, was without significance except that an older brother (case 2) had been suffering from "arthritis" for over seventeen years.

Examination.—Except for hypertension (170 systolic and 95 diastolic) and bilateral middle ear deafness, the general examination revealed nothing abnormal.

Neurologic Examination.—Neurologic signs were: spastic paraplegia in flexion, more pronounced on the right side, and flexion contracture of the right leg (at the knee); slight wasting of the intrinsic muscles of both hands, ataxia and slight decomposition of movement, with terminal tremor on the right side; generalized hyperreflexia (tendinous and periosteal), with bilateral ankle clonus and Babinski sign and unobtainable abdominal reflexes; notable impairment of the senses of vibration and position in all four extremities, the sense of vibration being more affected than the sense of position; questionable temporal pallor of the right papilla; weakness of the left internal rectus muscle; poor convergence of both eyeballs on looking at near objects; bilateral coarse horizontal nystagmus on lateral gaze and vertical nystagmus on upward gaze, and weakness of the left side of the face of supranuclear type. The psychiatric examination revealed a moderate tendency to euphoria.

Laboratory Data.—Lumbar puncture yielded normal fluid under normal pressure; there was no subarachnoid block. The Wassermann reactions of the blood and spinal fluid were negative; the mastic curve was flat. Examination of the blood and urine gave normal results. A roentgenogram of the vertebral column showed advanced productive spondylitis throughout.

Course of the Disease.—The patient was discharged from the hospital on April 18, 1940, with her condition unchanged. On Nov. 11, 1940 in another hospital, she was subjected to bilateral tenotomy of the hamstring and adductor muscles, anesthesia being induced with cyclopropane and oxygen. After this operation both lower extremities were placed in plaster of paris casts. Three days later she became psychotic. In two weeks her mental condition improved. Recent examination by one of us revealed that the neurologic status was unchanged. Psychiatric examination disclosed no gross abnormalities.

CASE 2.—S. F., the brother of the patient in case 1, a man aged 54, was admitted to the Montefiore Hospital on April 10, 1940 with complaints of difficulty in gait for seventeen years, weakness of the right hand for four years and tinnitus of the left ear for several months. He was well until the age of 37, when he began to experience a peculiar sensation in the left leg, "as if it were sinking in mud." Two years later his gait became unsteady, and he fell repeatedly. At about the same time there also appeared weakness and stiffness, at first of the lower and then of the upper extremities. The condition progressed gradually so that five years before his admission to the hospital walking became impossible and he was chair ridden. Six months before admission he was twice unable to urinate and on one occasion to defecate.

He stated that one of his sisters (case 1) had recently been a patient at the Montefiore Hospital because of "arthritis." Otherwise the family history was noncontributory.

Examination.—Except for bilateral middle ear deafness, scoliosis of the dorsal portion of the spinal column and bilateral talipes cavus, the general examination disclosed no noteworthy abnormalities. The blood pressure was 150 systolic and 100 diastolic; the pulse rate was 96 per minute.

Neurologic Examination.—Neurologic tests revealed: spastic paraplegia in flexion, only the toes being moved; spasticity of the right upper extremity and paresis of the left upper extremity; wasting of the intrinsic muscles of the hand and of both shoulder girdles; bilateral ataxia in the finger to nose test (it was impossible to determine how much of the ataxia was due to the incoordination and how much to weakness); generalized hyperreflexia (tendi-
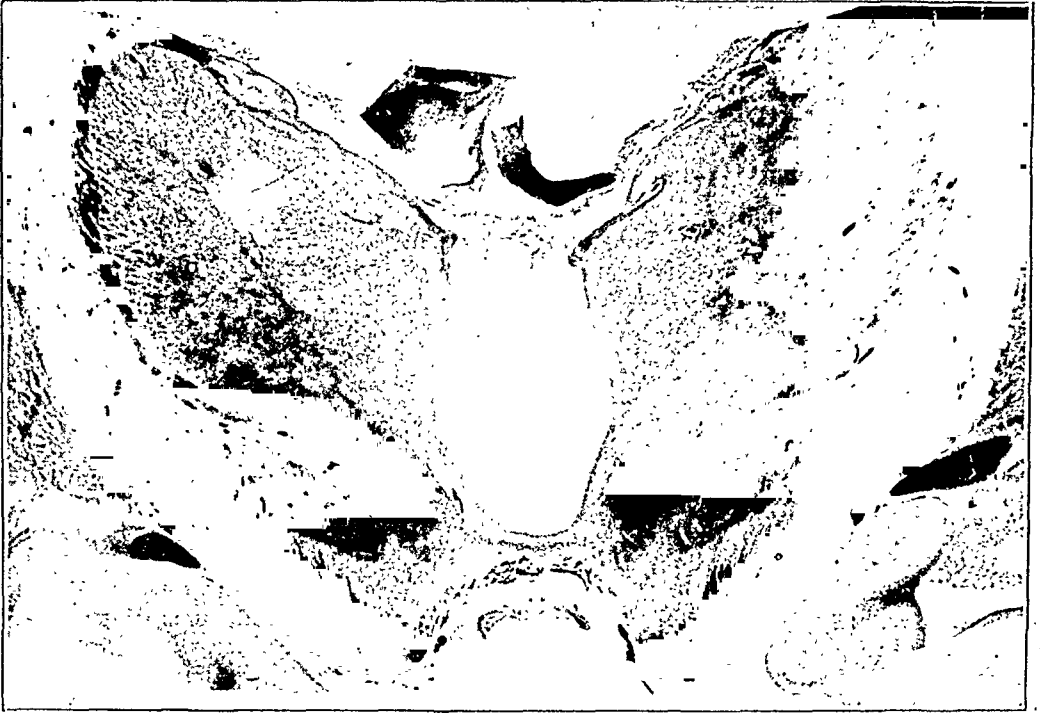
Fig. 1.—Plaques in the left medial and right lateral nuclei of the thalamus. Myelin sheath stain.

Fig. 2.—Plaques in the left vestibular and cochlear nuclei and at the level of the eighth nerve on the right side. Myelin sheath stain.

nous and periosteal) ; bilateral Babinski sign and absence of abdominal and cremasteric reflexes, and some impairment of the sense of position in the toes, loss of the vibratory sense from the toes up to the sixth dorsal segment and diminution of this sense in both hands.

Psychiatric examination showed that memory for past events was slightly defective.

Laboratory Data.—Lumbar puncture yielded normal spinal fluid under an initial pressure of 30 mm. of water; there was no subarachnoid block. The Wassermann reactions of the blood and spinal fluid were negative. The mastic curve was flat, and the total protein content was 48 mg. per hundred cubic centimeters. Examination of the blood showed moderate secondary anemia and lymphocytosis, with a count of 41 per cent. Urinalysis revealed a specific gravity of 1.008, a trace of albumin and innumerable white blood cells. Chemical studies of the blood revealed 37.5 mg. of urea nitrogen per hundred cubic centimeters. Gastric analysis disclosed absence of free hydrochloric acid even after an injection of histamine. The electrocardiogram showed low voltage. Roentgenographic examination of the chest revealed no abnormalities.

Course of the Disease.—The patient's condition remained unchanged until Jan. 3, 1941, when he suddenly became dyspneic, cyanotic and pulseless. He died seven hours later.

Necropsy.—Plaques were observed in the motor convolutions; in the thalamus (fig. 1) ; in the periaqueductal area; in the floor of the fourth ventricle, extending to the exit of the eighth nerve on the right side; in the vestibular and cochlear nuclei on the left side (fig. 2) ; in the nuclei of Goll and Burdach on the left side; in the nucleus of the descending portion
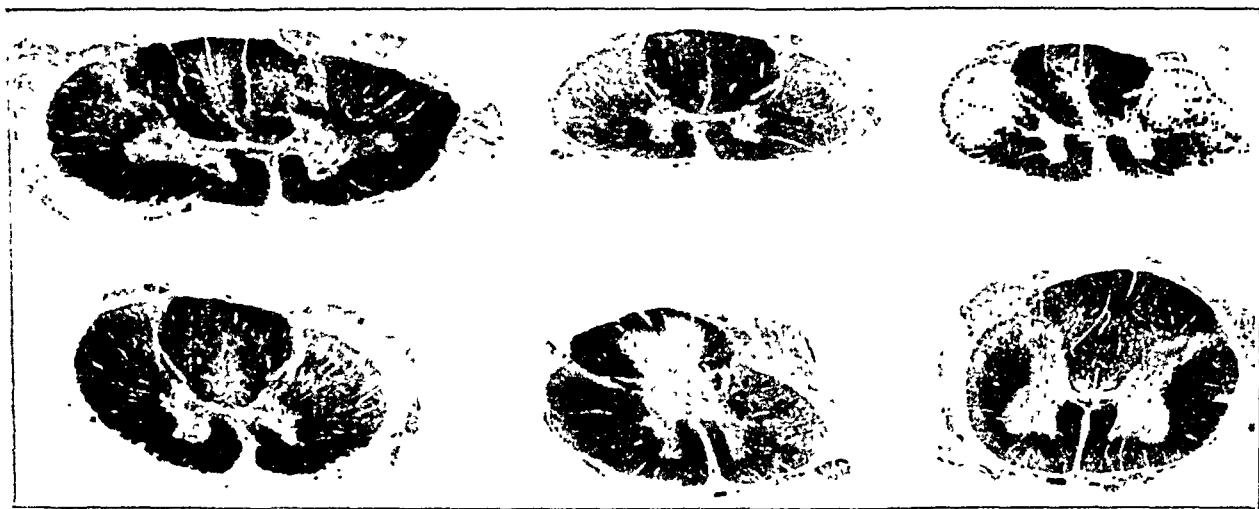
Fig. 3.—Plaques in the posterior column of the dorsal region of the cord, with slight descending degeneration. Myelin sheath stain.

of the left trigeminus nerve, some of the fibers of the medial lemniscus being caught, and in the posterior region of the lower dorsal portion of the cord (fig. 3).

COMMENT

The usual incidence and distribution of cases of multiple sclerosis are evidence that genetic factors are, in general, of little significance in producing this disease. However, the 2 cases we have reported, and similar instances in the literature, indicate that in a very small percentage of cases the influence of heredity must be considered.

SUMMARY

In a review of the literature on familial and hereditary factors in multiple sclerosis a few cases verified by necropsy were found. We report 2 additional cases of the disease in a brother and a sister, in 1 of which the diagnosis was verified at necropsy. We believe that in occasional cases hereditary factors may be of etiologic significance.

Dr. Charles Davison made the neuropathologic examination.

110 East Ninetieth Street.
451 West End Avenue.

News and Comment

DEPARTMENT OF PSYCHIATRY, McGILL UNIVERSITY

McGill University announces the creation of a department of psychiatry and, in association with the Royal Victoria Hospital, the establishment of an institute for research and teaching. Through the generosity of Sir Montagu and Lady Allan, a building and an extensive site have been provided.

The institute will contain fifty beds for patients suffering from early and acute psychiatric conditions. Facilities for intensive treatment are being set up. The development of research and treatment will be major objectives, and, with this in view, large and well equipped laboratories are to be provided.

The project is being supported both by the Rockefeller Foundation and the government of the Province of Quebec. Dr. D. Ewen Cameron has been appointed to the chair of psychiatry and will also be the director of the institute.

PENNSYLVANIA PSYCHIATRIC SOCIETY

The fifth annual dinner meeting of the Pennsylvania Psychiatric Society was held in Philadelphia on Oct. 7, 1943.

Mr. John Corcoran, noted radio news analyst, commentator and writer, spoke on the subject of "Today"; "The Referral Center for Selective Service in Philadelphia" was described by O. Spurgeon English, M.D., Philadelphia, and the presidential address was delivered by George J. Wright, M.D., of Pittsburgh.

Officers for 1943-1944 were elected as follows: president, Ralph L. Hill, M.D., Wernersville, Pa.; president-elect, George W. Smeltz, M.D., Pittsburgh; Secretary-Treasurer, LeRoy M. A. Maeder, M.D., Philadelphia.

Councillors elected were: Leslie R. Chamberlain, M.D., Danville, Pa.; Theodore L. Dehne, M.D., Philadelphia; John N. Frederick, M.D., Pittsburgh; Ronald B. McIntosh, M.D., Selinsgrove, Pa.; John F. Stouffer, M.D., Philadelphia; John I. Wiseman, M.D., Torrance, Pa., and George J. Wright, M.D., Pittsburgh.

Auditors elected were: Robert S. Bookhammer, M.D., Philadelphia; Gomer S. Llewelyn, M.D., Mayview, Pa., and Howard K. Petry, M.D., Harrisburg, Pa.

Address: LeRoy M. A. Maeder, M.D., secretary-treasurer, Chancellor Hall, 206 South Thirteenth Street, Philadelphia 7.

Obituaries

CHARLES MACFIE CAMPBELL, M.D.
1876-1943

Courage, independence and wit were combined in Charles Macfie Campbell to make him a leader in neuropsychiatry with a host of friends. He played the game to the end, like the sound scholar and trained British sportsman he was. Even those closest to him knew nothing of his angina until shortly before his death. on Aug. 7, 1943. Through these last years he asked no relief from responsibility and work; he did not spare himself, and his exuberance did not lessen. The end came twenty-three days before he was to have become professor emeritus. That is the way he would go!

Born in Scotland in 1876, he attended the George Watson Boys' College to prepare himself for Edinburgh University, where he matriculated in 1893, graduating in 1897 with the degree of Master of Arts and first class honors in philosophy. He had spent two summers abroad learning French and German; so he entered his medical studies at Edinburgh well prepared. In 1900 he took the degree of Bachelor of Science, with distinction in anatomy, physiology and anthropology. After a summer at the Salpêtrière, he continued his medical studies in Edinburgh and graduated in 1902, *summa cum laude,* with the degrees of M.B. and Ch.B., receiving the McCosh Graduation and Medical Bursaries. Thereafter he did graduate work abroad—in Paris, under Marie and Babinski, and in Germany, under Erb, Hoffmann and Kraepelin. Returning to the Royal Edinburgh Infirmary in 1903, he became resident on the service of Alexander Bruce. In 1904 he came to America as a member of the staff of the Pathological Institute of the New York State Hospital. In 1907 he returned to Scotland for a year as assistant physician at the Royal Edinburgh Asylum and became a member of the Royal College of Physicians of Edinburgh. The next year he was asked to become an associate at the new Psychiatric Institute in New York and returned to America for the rest of his professional career. Here he began his long association with Adolf Meyer, both at the Institute and as a teacher at Cornell University Medical College. In 1911 he was awarded the degree of Doctor of Medicine from Edinburgh for his thesis on "Focal Symptoms in General Paralysis." For two years he was a psychiatrist at Bloomingdale Hospital, White Plains, N. Y., while preparing to go to Baltimore with Meyer. In 1913 he moved thither to become assistant professor of psychiatry at Johns Hopkins University and associate director of the Phipps Psychiatric Clinic. Here he was a brilliant teacher, especially for the resident staff. He and Mrs. Campbell (herself a doctor of medicine from Edinburgh) lived in a lovely house at Windsor Hills, and here the assistants and interns often came for delightful hours with the growing Campbell family. Happy years for all and great days at the Johns Hopkins Hospital, with Abel, Howell, Halstead, Mall and Welch keeping up the tradition of the founders and Howland, Janeway and Meyer at their best! But the war soon cast its shadow, and work at the Phipps Clinic became more strenuous, with fewer men to help and groups of Army officers to be trained in neuropsychiatry. For this Campbell became a "civil surgeon" in 1917, and later, in 1918, he joined the United States Army as a private in order

to become a citizen and obtain a commission. The armistice interrupted this plan, and he never received his commission.

In 1920 came the call to the chair of psychiatry at Harvard Medical School, combined with the directorship of the Boston Psychopathic Hospital. He gladly accepted these responsibilities, for which he had so long and carefully trained himself, but he left with regret the genial setting of Baltimore, where he and Mrs. Campbell had made so many friends. The new assignment was arduous; to take the place of such a young and beloved man as Southard was a complicated and difficult task, but Campbell soon made his place and took leadership. His twenty-three years of service to Harvard and the Psychopathic Hospital were active and happy, with multiplying responsibilities and interests both in psychiatry and in the academic circles in Cambridge, where he was welcomed as a scholar. He was a liberal in spirit and thought, and as free from prejudice as can be expected of a human being; only one prejudice can be detected in his life: a complete intolerance toward deceit, opportunism and appeasement. He was a strict disciplinarian, expecting no evasions from either his subordinates or his peers, but he had an understanding of the weaknesses and frailties of man, with more than ready willingness to give a helping hand to one who had failed along the way. He was not an indiscriminate hale-fellow-well-met, but no more companionable man could be imagined. A gifted speaker, with the facility to turn a word or phrase in fun, with a twinkle of the eye and a warming smile, he was a leader at medical meetings and banquets. He had a broad interest in the cultural side of life, especially in literature and philosophy. A rapid reader with a retentive memory, with an ability to recall quickly matters appropriate to the conversation of the moment, he was an unusually interesting conversationalist. No one ever heard him say a word in praise of himself, nor did he encourage others to praise or flatter him. Sympathetic to others, he never sought sympathy for himself, never shared problems or woes with others. There were no soft spots in his firm yet lively character.

Perhaps his most important contribution to psychiatric thought is found in his article entitled "The Mechanism of Some Cases of Manic-Depressive Excitement" (*M. Rec.* **85**: 681, 1914). This was essentially the first American declaration of the importance of the psychologic and social factors to be considered in the study of patients with affective disorders. Certainly this treatise gave expression to an illuminating point of view about the effect of life situations on personality; it considered the dynamic and genetic possibilities in the production of mental disorder. It announced the path which Dr. Campbell was to travel in his clinical investigations during the next thirty years. It shows his meticulous consideration of the patient in the setting in which he lived, thought, felt and worked. Campbell was one of the earliest contributors in the field of psychiatry to recognize and to stress the importance of emotions, instinctive drives and personal problems in the causation of the syndromes which there is now a tendency to label psychosomatic disorders. At the same time he was one of the first to point out the relation of psychiatry to problems of general medicine.

His most definite interest was in the problem of schizophrenia, which he studied intensively during all his Boston period. It is greatly to be regretted that the results of these studies have not been published. It may be assumed that he planned to use the years following his retirement in analyzing this material and in presenting the results of his studies.

Even more significant than his numerous writings was the effect of his teaching of the young men and women specializing in psychiatry. To them he imparted his deep faith that the understanding of the individual patient was the foundation

on which all psychiatric study must rest and the basis for the therapeutic approach. Day after day and year after year he pointed out to succeeding groups of students and resident physicians the importance of a close physician-patient relationship.

CHARLES MACFIE CAMPBELL, M D.
1876-1943

and always during the thousands of days of this procedure there was enthusiasm for any discovery that helped to explain the meaning of the patient's reactions. His own continuing fascination with the clinical approach could not help being

contagious, and this influence has been carried to all parts of the country by his many pupils.

He was a member of the following scientific societies: the American Medical Association; the New York Psychiatric Society; the Association for Research in Nervous and Mental Disease; the Boston Society of Psychiatry and Neurology (president in 1924); the Eugenic Research Association; the American Psychopathological Association (president in 1918); American Neurological Association; the American Psychiatric Association (president in 1937); the New England Society of Psychiatry; the Massachusetts Psychiatric Society (president in 1935); the History of Science Society; the American Association of Hospital Social Workers; the British Medical Association; the Royal College of Physicians of Edinburgh, and Sigma Xi.

He was a member of the American Board of Psychiatry and Neurology, serving as vice president from its organization in 1934 and as its president since 1941. He was a member of the Committee on Psychiatry and the National Research Council. He was psychiatrist to the Medical Advisory Board of Selective Service.

His bibliography of scientific publications includes more than seventy separate items, of which five were in book form. It is significant that his earliest publications dealt with neuropathologic and neurologic subjects and that his writings subsequent to 1911 were devoted to matters more definitely psychiatric.

HARRY C. SOLOMON, M.D.
STANLEY COBB, M.D.

Abstracts from Current Literature

Anatomy and Embryology

TERMINATION OF THE BRACHIUM PONTIS. FRED A. METTLER and ALBERT J. LUBIN, J. Comp. Neurol. **77**: 391 (Oct.) 1942.

Mettler and Lubin interrupted the brachium pontis in 7 cats without involving the cerebellum or its blood vessels. After two weeks the cerebellums were treated by the Cajal technic and the climbing and mossy fibers studied. No change occurred in the climbing fibers. The mossy fibers showed notable abnormalities. The loss in these fibers was estimated to be at least 50 per cent and was seen both in the vermis and in the hemispheres, especially in the ipsilateral one. Toward the anterior lobe and the posterior parts of the vermis the number of mossy fibers was nearly normal.   ADDISON, Philadelphia.

THE PYRAMIDAL TRACT: A FIBER AND NUMERICAL ANALYSIS IN A SERIES OF NON-DIGITAL MAMMALS (UNGULATES). A. M. LASSEK, J. Comp. Neurol. **77**:399 (Oct.) 1942.

Lassek studied the pyramidal tract at the uppermost part of the medulla in the cow, deer, goat, hog, mule and sheep. The medullas were prepared by a silver technic to show fibers. The area, expressed in square millimeters, and the number of fibers computed were as follows: cow, 2.97 sq. mm., and 540,000 fibers; deer, 2.89 sq. mm. and 490,000 fibers; goat, 1.98 sq. mm. and 260,000 fibers; hog, 1.8 sq. mm. and 210,000 fibers; mule, 3.74 sq. mm. and 412,000 fibers, and sheep, 1.42 sq. mm. and 238,000 fibers. The maximum caliber of the axons in ungulates was about one-half that in man. The fibers in the larger animals were no larger than those in the smaller animals.   FRASER, Philadelphia.

THE STRIATE AREA OF PRIMATES. GERHARDT VON BONIN, J. Comp. Neurol. **77**:405 (Oct.) 1942.

Von Bonin studied silver and Golgi preparations of the area striata of man, macaque, mangabee, orang, Cebus, Tarsius, chimpanzee and Galago. He then analyzed the numbering of the layers in this area according to Ramón y Cajal, Brodmann and Lorento de Nó. Brodmann's layer IVA is considered by von Bonin as layer iiiB because it is above the stripe of Gennari, which is homologous to layers iva and ivb of the parietal cortex. Von Bonin's layers iva and ivb contain the stripe of Gennari and are layers 4 and 5 of Cajal. Layers V and VIA of Brodmann become layers va, vb and vc of von Bonin. Stratification was simplest in Galago and most elaborate in Tarsius. A characteristic area, the margo magnocellularis, was noted in chimpanzee, macaque and Cebus. The visual area of man was comparatively primitive in its pattern of lamination, but its supragranular layers were better developed than those in lower primates. The complexity of its pattern appears to be proportional to the size of the striate area in relation to that of the whole cortex.

FRASER, Philadelphia.

PROBST'S TRACT IN THE CAT. KENDALL B. CORBIN, J. Comp. Neurol. **77**:455 (Dec.) 1942.

Corbin studied the origin and course of that portion of the mesencephalic root of the fifth nerve which descends caudal to the exit of the trigeminal nerve in the cat. The mesencephalic root was located by oscillographic recording of potentials elicited by stretch of the masticator muscles. Small lesions were then placed by means of the stereotaxic instrument so as to interrupt the root at various levels from the motor nucleus of the fifth nerve to the region of the oculomotor nucleus. The animals were allowed to live for ten days and the medulla, pons and mesencephalon prepared by the Marchi technic. Fibers of Probst's tract arose from the ventral one fourth of the mesencephalic root of the fifth nerve; its cells of origin appeared to be scattered throughout the extent of the nucleus of this root. The tract descended midway between the dorsal tip of the spinal tract of the fifth nerve and the genu of the seventh nerve close to the salivatory nuclei. It finally was located immediately ventral to the nucleus of the solitary tract. At the level of the dorsal motor nucleus of the vagus nerve the tract gradually disappeared. No collaterals were seen passing to the facial nerve or its nucleus or to the vestibular nerve. Corbin suggests that because of the intimate anatomic

relation between Probst's tract and the salivatory°and dorsal nuclei of the vagus nerve and the nucleus of the solitary tract there is a functional association concerned in masticatory, salivary and gustatory reflexes.   ADDISON, Philadelphia.

THE THALAMUS OF THE SHEEP: CELLULAR AND FIBROUS STRUCTURE AND COMPARISON WITH PIG, RABBIT AND CAT. JERZY E. ROSE, J. Comp. Neurol. **77**:469 (Dec.) 1942.

Rose studied the thalamus of the sheep in transverse, horizontal and sagittal series stained for myelin or Nissl substance. He divides the thalamus into the epithalamus, the thalamus dorsalis and the thalamus ventralis. The epithalamus is a single embryonic area from which develop the paraventricular complex, the pretectal group and the habenular complex. From the dorsal thalamus originate the anterior, medial, ventral and dorsolateral nuclear groups; the medial geniculate body; the dorsal nucleus of the lateral geniculate body, and practically all the interstitial nuclei. The ventral thalamus gives origin to the reticular complex and the ventral nucleus of the lateral geniculate body.   ADDISON, Philadelphia.

STUDIES ON THE DIENCEPHALON OF THE VIRGINIA OPOSSUM: III. THE THALAMO-CORTICAL PROJECTION. DAVID BODIAN, J. Comp. Neurol. **77**:525 (Dec.) 1942.

In addition to normal series of the brain of the opossum, Bodian studied 17 brains in which there was retrograde thalamic degeneration following cortical injury by thermocautery or scalpel. Three to six weeks after hemidecortication residual cells were scarce in all but the subparataenial, the parafascicular and the medial geniculate nuclei. Localization was precise with respect both to the projection of specific nuclei of the dorsal thalamus and to the projection of segments of most of these nuclei. Contiguous thalamic nuclei tended to project to contiguous cortical fields. Midline and commissural nuclei showed no degeneration.

FRASER, Philadelphia.

THE DECUSSATION OF MAUTHNER'S FIBERS IN FUNDULUS EMBRYOS. JANE M. OPPEN-HEIMER, J. Comp. Neurol. **77**:577 (Dec.) 1942.

Oppenheimer transplanted the Mauthner cells in embryos of Fundulus during gastrulation. In 8 embryos these cells were located either ectopically within the host brain or in comparatively discrete brain grafts that effected nerve connection with the host brain, and the fibers descended near their usual path but in general failed to cross. In embryos in which supernumerary Mauthner cells were located abnormally far laterally or unusually far anteriorly the supernumerary fibers remained ipsilateral. Oppenheimer suggests that the decussation occurs in normal and in experimental material only if the fibers reach the decussation level at a time specifically related to the occurrence of other particular events at this level, these events involving perhaps the differentiation of some of the great longitudinal pathways.

FRASER, Philadelphia.

Neuropathology

A REVIEW OF BRAIN PATHOLOGY IN THE CONVULSIVE DISORDERS. WILLARD W. DICKERSON, Am. J. Psychiat. **99**:679 (March) 1943.

Dickerson tabulated his observations, both gross and histologic, on examination of the brains of 150 patients suffering from convulsions. In one third of the brains no abnormalities could be seen, and the condition was considered idiopathic. Trauma was found to play a small role, while malformations of the cytoarchitectural type were frequently encountered. Dickerson could attach no etiologic significance to the pathologic changes.

FORSTER, Philadelphia.

A CASE OF BILATERAL LESIONS OF AREA 19 OF BRODMANN. ARNOLD P. FRIEDMAN and J. M. NIELSEN, Bull. Los Angeles Neurol. Soc. **7**:209 (Dec.) 1942.

Friedman and Nielsen report a case in which the patient suddenly became blind and lost the power of revisualization. Though the parietal lobes were intact, the patient was unable to revisualize objects through the sense of touch. Autopsy revealed lesions in the occipital lobes affecting area 19 of Brodmann on each side.   LESKO, Bridgeport, Conn.

RECOVERY OF RABIES VIRUS FROM BRAIN OF UNDIAGNOSED CASE. M. SCHAEFFER and G. LEIDER, J. Lab. & Clin. Med. **27**:1263 (July) 1942.

Schaeffer and Leider recovered rabies virus in a case in which the cause of death was obscure. The presence of virus in the brain in this undiagnosed case was established by

animal passages, by demonstration of Negri bodies in the brains of inoculated animals and by immunologic methods. After the recovery of virus, further investigation revealed a history of dog bite and other data pertinent to rabies in a case in which the antemortem diagnosis was "psychoneurosis and acute anxiety." The need exists to be ever mindful that atypical cases may occur in communities in which rabies is endemic.   J. A. M. A.

MYASTHENIA GRAVIS, INCLUDING CASE REPORT AND NEUROLOGICAL AUTOPSY. HENRY G. HADLEY, J. Nerv. & Ment. Dis. **97**:6 (Jan.) 1943.

Hadley reports an autopsy on a patient with typical myasthenia gravis who died of respiratory failure. Gross examination of the brain revealed softening of the pons. Microscopic examination showed vascular engorgement and perivascular hemorrhages in the thalamus and hypothalamus, especially in the mamillary bodies, and great dilatation of the perivascular spaces in the tegmentum of the pons. In two or three areas under the ependymal lining of the aqueduct there was an active proliferative process, with formation of nodules. Similar, less mature, nodules were noted elsewhere, and early subependymal changes were seen in a section through the fourth ventricle and the restiform body. The blood vessels of this region were engorged and the perivascular spaces dilated. The cells of the olivary nucleus were more shrunken, pyknotic and sparse than usual. Little change was seen in a section of skeletal muscle and in the pituitary gland.   CHODOFF, M. C., A. U. S.

AMYOTONIA (MYATONIA) CONGENITA: OPPENHEIM'S DISEASE. G. B. HASSIN, J. Neuropath. & Exper. Neurol. **1**:351 (Oct.) 1942.

Hassin reports the clinical and pathologic changes in the case of a 6 month old Italian girl who presented the clinical picture of amyotonia congenita. She had had extreme weakness of the lower extremities since birth and was unable to sit up because of weakness of the muscles of the neck and back. The legs were motionless and extended but showed no atrophy. All tendon reflexes were absent. She died at the age of 7 months—the exact age at which a sibling had died of "paralysis."

Histologic examination of the spinal cord revealed scarcity of nerve cells throughout, especially in the lumbosacral region. Here some of the cells were reduced in size, appeared homogeneous and contained scant Nissl substance at the periphery. Occasional cells showed satellitosis and neuronophagia. A striking feature of the microscopic picture was the presence of numerous heterotopic nerve cells in the ventral spinal column, the posterior spinal roots, the pia and the subarachnoid space. The white substance of the cord contained increased numbers of microgliocytes, oligodendrocytes and cytoplasmic astrocytes. There was less myelin in the pyramidal tracts, the posterior column, the lateral limiting zone and the ventral root zone than in the marginal areas, the spinocerebellar tracts and the ventral pyramid. The peripheral nerves appeared normal.

Microscopic study of muscle showed that in some bundles the fibers appeared normal, but in others there were hypoplastic muscle fibers interspersed with bundles of unripe embryonic fibers, and occasional hypertrophic fibers, some of which were in a state of regression.

Similar changes, confined to the "peripheral neuromuscular neuron," have been described in cases of Werdnig-Hoffmann disease (infantile progressive muscular atrophy). It is thought that in both diseases there is retarded development of the anterior horn cells, myelin sheaths and muscles. While Hassin feels that a differential diagnosis of either disease cannot be made from the microscopic appearance of the muscles or the spinal cord, it is noteworthy that the numerous heterotopic nerve cells observed in this case of amyotonia congenita have not been described in cases of Werdnig-Hoffmann disease.   CAMPBELL, Philadelphia.

SCARLATINAL ENCEPHALOMYELITIS. N. W. WINKELMAN, J. Neuropath. & Exper. Neurol. **1**: 363 (Oct.) 1942.

Because encephalomyelitis following scarlet fever is considered rare, Winkelman reports the clinical and pathologic observations in a case which appears unique in the severity of its neuropathologic changes. A 9 year old Negro girl manifested cerebral symptoms seven days after the onset of scarlatina. Competent staff members, who had treated many Negro patients with contagious diseases, stated that the rash was typical of that associated with scarlet fever. In addition to nuchal rigidity, the patient showed clinical evidence of widespread involvement of the cerebrum, brain stem and spinal cord. The cerebrospinal fluid contained 150 to 280 cells per cubic millimeter, over 90 per cent being lymphocytes. The patient became increasingly stuporous, pulmonary edema developed, and she died ten days after the onset of the illness.

Grossly, the brain showed extreme congestion and some edema but no softenings or hemorrhages. Microscopic examination revealed dilatation of the subarachnoid space, in which were

congested blood vessels, some free blood and numerous histiocytes containing pigment and debris. Practically all the cortical nerve cells displayed extreme changes, ranging from ischemia to complete destruction. A few rod cells were present. There was notable increase in glia cells, the predominating form being the fibrillary astrocyte. The cytoarchitecture of the cortex was not greatly disturbed.

Both the gray and the white matter throughout the cerebrum, the brain stem and the spinal cord showed diffuse inflammatory involvement. Practically every small blood vessel was prominent because of swelling and proliferation of the endothelium, dilatation and congestion, or perivascular infiltration with lymphocytes and plasma cells, such areas being frequently surrounded by microglia cells. This infiltrative process was most prominent in the subcortex, in which perivenous necrosis was conspicuous. Many of the veins contained coagulated blood, and in a few, fibrin formation was beginning. In the brain stem the same general vascular and glial reactions were present, the process being more intense in the white matter. The spinal cord showed extensive demyelination, notable loss of ventral horn cells, glial overgrowth, and blood vessels "heavily mantled with lymphocytes, plasma cells, phagocytes and microglia."

The author emphasizes that in this case "the clinical condition was totally different from the usual mild recoverable neurologic complications seen infrequently in scarlet fever," which complications have been thought to be due to the toxins of the streptococcus. He concludes that "the central nervous complications were not the result of the 'scarlatinal organism itself,' but developed from the release by the streptococcus of a virus lying dormant within the central nervous system."

CAMPBELL, Philadelphia.

Psychiatry and Psychopathology

IRRESPONSIBILITY OF JUVENILE DELINQUENTS. D. A. THOM, Am. J. Psychiat. 99:330 (Nov.) 1942.

Thom discusses the group of juvenile nonconformists who are well endowed intellectually and are not suffering from a recognized type of mental illness but who are guilty of serious crime and are considered as incorrigible. As a case in point, he details that of a 15 year old boy who since the age of 3 had been a problem child, his offenses becoming increasingly serious and culminating in an atrocious murder. In the report of the psychiatrists who examined this boy the need was stressed for some rational medical and legal handling of the problem of the constitutional psychopath. Thom points out that the judiciary recognizes only frank mental disease and obvious mental deficiency as mitigating factors. Psychiatrists, on the other hand, have frequently come to consider the psychopath as irresponsible. The necessity for joint action of the legal and the medical forces is obvious.

FORSTER, Philadelphia.

CONSIDERATION OF RESULTS WITH PSYCHOANALYTIC THERAPY. C. P. OBERNDORF, Am. J. Psychiat. 99:374 (Nov.) 1942.

Oberndorf points out the difficulties in statistical evaluation of the results of psychoanalytic therapy. Much of the material is unavailable, as it is in private files. Moreover, the theoretic standards for evaluation of results are difficult to delimit. The statistics available indicate that 60 per cent of all patients were recovered or improved, which figure coincides with reports from institutions not employing intensive psychoanalytic therapy. Oberndorf points out that brief treatment along strict psychoanalytic lines frequently produces good results. He indicates, also, that there has been no correlation between the length and depth of analysis, on the one hand, and the permanency and quality of the result, on the other. The best results are encountered in treatment of the anxiety neuroses and conversion hysterias; the poorest results with intellectual narcissistic persons and manic-depressive patients. Oberndorf ·believes that more patients have avoided hospitalization by means of psychoanalysis than have been hospitalized after analysis.

FORSTER, Philadelphia.

INVESTIGATION OF THE EFFECT OF INHALATION OF 9 PER CENT OXYGEN FOR 20 MINUTES IN NON-PSYCHOTIC AND SCHIZOPHRENIC MALE SUBJECTS. WILLIAM L. HOLT JR., Am. J. Psychiat. 99:406 (Nov.) 1942.

Holt subjected 13 male schizophrenic patients and 12 normal male controls to twenty minute periods of breathing a mixture of 9 per cent oxygen and 91 per cent nitrogen. The neurologic status of each subject was checked at five minute intervals during the procedure. Alterations of the plantar responses occurred in 1 patient and in 1 control. Under anoxemic conditions the schizophrenic patients had smaller pupils than the controls and manifested less miosis and less reaction to light. They also showed only slight impairment of consciousness, while 3 of the control subjects had considerable impairment.

FORSTER, Philadelphia.

AUTONOMIC NERVOUS SYSTEM FUNCTION IN CHILDREN WITH BEHAVIOR PROBLEMS AS MEASURED BY THE PAROTID SECRETORY RATE. R. S. LOURIE, S. E. BARRERA and E. I. STRONGIN, Am. J. Psychiat. **99**:419 (Nov.) 1942.

Lourie, Barrera and Strongin measured the secretory rate of the parotid gland in children with behavior problems. The method is a measure of the parasympathetic activity. Ninety-seven children with behavior problems were studied; 45 of them had an abnormally high secretory rate. Follow-up studies of the clinical condition from six months to a year later indicated a higher incidence of improvement for those who had normal secretory rates. The authors conclude that while the parotid secretory rate appears to be a criterion of parasympathetic activity in children, it should not be considered an absolute index.

FORSTER, Philadelphia.

THE PSYCHONEUROTIC IN THE ARMED FORCES. NICHOLAS MICHAEL, Am. J. Psychiat. **99**: 651 (March) 1943.

Michael points out that the psychoneurotic person is constitutionally unfit for military service and that despite the screening at induction centers such men are still entering the armed services. He indicates the role the family physician can play in the deferment of such persons. Michael concludes that while a few psychoneurotic men can be retained in the services during peacetime, and apparently do good work on limited duty, as a general rule their use is questionable.

FORSTER, Philadelphia.

FORENSIC ISSUES IN THE NEUROSES OF WAR. A. KARDINER, Am. J. Psychiat. **99**:654 (March) 1943.

Kardiner points out that the psychiatric picture presented by persons exposed to the hardships of war is necessarily confusing, since the external agent is operating on personalities of diverse nature. Thus, not a disease entity but a traumatic syndrome is to be expected. The neuroses in which the traumatic syndrome occupies the façade of the symptoms are considered as traumatic. In this group of neuroses the symptoms are divisible into (1) defensive rituals, (2) autonomic disorders, (3) sensory-motor disorders and (4) syncopal episodes. The characteristics essential to all four types include (1) characteristic dream life, (2) alteration of disposition and character, (3) typical inhibitions and (4) a typical Rorschach picture. Kardiner stresses the importance of an understanding of the relation between the psychopathologic features and the origin and symptoms of the neurosis. This neurosis limits the patient's action and psychophysical resources, with resulting reduced capacity for work and the issue of compensation. Early therapy is necessary for the prevention of intractability. Compensation should be reserved until after two years of unsuccessful therapy.

FORSTER, Philadelphia.

THE INFLUENCE OF INDIAN AND NEGRO BLOOD ON THE MANIC-DEPRESSIVE PSYCHOSIS. SIEGFRIED FISCHER, J. Nerv. & Ment. Dis. **97**:409 (April) 1943.

Fischer states that the distribution and type of manic-depressive psychosis vary among different peoples, probably in accordance with constitutional differences and body structure. He discusses the influence of Indian and Negro blood on this psychosis. The patients studied, 12 in all, included 5 mestizos (with a mixture of Indian and white blood) and 7 mixed descendants of Indians, white persons and Negroes. Among the mestizos, manic phases of the psychosis prevailed; depressive states were infrequent and of short duration. The intensity of symptoms in both phases was slight. In the manic state, the patients exhibited slight elevation of mood and some gaiety, though they were as frequently irritable and troublesome. Hyperactivity was mild; there was never a flight of ideas, and there was little distractibility or agitation. In the depressive state, affect was shallow, and there were no strong suicidal drives. The patients never appeared hopeless. As in the mestizos, among the descendants of white persons, Indians and Negroes the depressions were relatively infrequent and of low intensity, and the danger of suicide was negligible. The low incidence of suicides is in accord with experience generally in the Republic of Panama, where the number of suicides is insignificant. Manic states among patients of mixed white, Negro and Indian blood were more typical than those seen among mestizos. Elevation of mood was great, and a slight flight of ideas and distractibility were noted. The more intense the manic state, the more distinct were the physical negroid features, but the true mania seen in white persons was never encountered. The author feels that Indian blood causes extenuation of symptoms in the manic state, while mixture with Negro blood neutralizes to a certain extent this effect. The influence of this factor is not noted in the depressive states, since depressions are not characteristic of either the Indian or the Negro.

CHODOFF, Langley Field, Va.

TWO FACTORS IN THE PROGNOSIS OF ALCOHOLISM. JOHN M. NAGLE, Psychiatric Quart. **16**:632 (Oct.) 1942.

Nagle asserts that the consumption of alcohol in beverage form is entirely a matter of personal equation. Because of this premise some patients must be subjected to reeducation directed along two lines: (*a*) the ability to practice self control, and (*b*) a knowledge of one's maximum tolerance. The latter factor is brought to the patient's attention in the form of the alcohol susceptibility test, which is a simple procedure to evaluate the susceptibility of the nerve tissue to chemical ethyl alcohol.   LESKO, Bridgeport, Conn.

PSYCHOPHYSIOLOGY OF BLOOD PRESSURE: I. PERSONALITY AND BEHAVIOR RATINGS. J. A. HAMILTON, Psychosom. Med. **4**:125 (April) 1942.

The studies recorded by Hamilton were based on the use of the methods and statistics of experimental psychology for the purpose of examining personality and behavior characteristics of young persons with elevated blood pressure. The main criterion for the selection of experimental and control groups was the systolic blood pressure, with arbitrary level of 138 mm. being used in separating the two groups. A single determination of blood pressure during routine physical examination was the sole factor defining and differentiating experimental and control groups. An attempt was made to study a wide range of psychologic variables in such a way as to yield quantitative data regarding the subjects. Among the psychologic tests were Harsh's annoyance inventory, Allport's A-S reaction study and McFarland and Seitz's P-S inventory. A life history questionnaire was also utilized, and the results obtained from all studies were subjected to statistical analysis.

The results indicated that persons with elevated blood pressure as a group exhibited tendencies toward decreased physical and social activity. They were inclined to move and walk more slowly and showed a tendency to avoid exercise and sports. They were somewhat less dominant and self assertive, had fewer friends and were more susceptible to anger. Blushing and palpitation after exercise were the chief symptoms reported.

Hamilton concludes that no evidence has been found in his varied tests which would support the contention that persons with elevated blood pressure are neurotic, unstable or physically hyperactive. However, it is noteworthy that the observations reported deal only with those aspects of personality and behavior which may be observed by the subject or his associates.   SCHLEZINGER, Philadelphia.

RELATION BETWEEN THE ELECTRICAL ACTIVITY OF THE CORTEX AND THE PERSONALITY IN ADOLESCENT BOYS. J. R. GALLAGHER, E. L. GIBBS and F. A. GIBBS, Psychosom. Med. **4**:134 (April) 1942.

Gallagher, Gibbs and Gibbs report on a group of 200 boys between 14 and 15 years of age selected at random from a private school and considered to be superior to the general population of the same age level in regard to their capacity to do school work. An attempt was made to determine what relation exists between the electrical activity of the cortex and deviations in personality. The personalities were classified as poor, average and good. Traits indicating "poor" personality were seclusiveness, shyness, excessive nervousness, extreme irritability, marked emotional instability, eccentricities and asocial behavior.

The electroencephalograms were analyzed primarily on the basis of frequency differences and were not classified as to the amount of alpha activity. No rigid relation could be determined between personality and electrical activity of the cortex. Nevertheless, it appears that if the electrical activity of the cortex falls within certain normal limits, the chances that the personality will be normal are increased. The deviations from the norm observed in the electroencephalograms of boys with "poor" and those in the electroencephalogram of boys with "good" personalities were in many cases identical, but cortical activity which is unusually slow is more likely to be associated with a "poor" personality, while cortical activity which is unusually fast is more likely to be associated with a "good" personality.   SCHLEZINGER, Philadelphia.

THE EFFECT OF DRUGS ON BEHAVIOR AND THE ELECTROENCEPHALOGRAMS OF CHILDREN WITH BEHAVIOR DISORDERS. D. B. LINDSLEY and C. E. HENRY, Psychosom. Med. **4**:140 (April) 1942.

Lindsley and Henry report on the electroencephalograms and behavior ratings of 13 children with behavior disorders who were studied over a period of six weeks. Amphetamine, phenobarbital and diphenylhydantoin sodium were used, and the results show that the behavior improved notably with amphetamine medication. Decided improvement of behavior also

occurred with diphenylhydantoin, but this drug was less effective than amphetamine. Pheno-barbital when given after a period of amphetamine medication caused exacerbation of symptoms, but when given after an initial control period it produced insignificant changes in behavior.

The electroencephalograms showed a number of statistically significant changes, but these were not pronounced and were not proportionate to the changes in behavior produced by the various drugs. The electroencephalographic changes were not always consistent for any one subject, for any one area of the head or for any one drug, when similar changes in behavior were noted. Therefore, the authors conclude that behavior disorders in children presumably have some relation to the abnormalities· observed in the electroencephalograms, but that improvement in behavior may occur without any essential modification in the abnormal electrical activity of the cortex.   SCHLEZINGER, Philadelphia.

ALCOHOLISM AND INDUCTION INTO MILITARY SERVICE. ABRAHAM MYERSON, Quart. J. Stud. on Alcohol **3**:204 (Sept.) 1942.

Myerson describes the types of alcoholic addicts examined by the induction board and classifies them as follows: (1) Saturday night drinkers. This group consists of men who work hard physically, who drink a few beers or whiskies daily but who on Saturday night get "stinko" and recover in time to go to work on Monday. The Boston group of psychiatrists believe that this type of heavy drinker is good military material. (2) Party drinkers. This group of heavy drinkers is also considered to be good military material. It is composed of men who attend parties two or three times a week, get tight frequently, are able to go to work the next day and abstain from drinking until the next party. (3) Spree drinkers. This group consists of men who, by the nature of their work, are subject to enforced sobriety and who make up for it by a long spree. When they are satiated they go back to work. The author divides pathologic sprees into two types: (a) that in which the drinker falls into a state of depression, either cyclothymic or as part of a periodic neurosis, and drinks until the depression or neurosis disappears, and (b) that in which the drinker goes without drinking for a long period, then suddenly takes the first drink and does not end until his money runs out or he is arrested or hospitalized. These drinkers are not accepted for the service. (4) Drinkers with social neuroses. This class of alcoholic addicts consists of men who, because of their bodily structure or functions feel self conscious, this preoccupation resulting in fears and phobias. (5) The sot. This is the most common type of draftee rejected for chronic alcoholism; he is more commonly known as the bayso bum, or the old soak. Alcohol to this patient is an end in itself—the primary purpose of existence and not an escape or a way of softening life's rigors.   LESKO, Bridgeport, Conn.

SOME CASUAL DATA ON DRINKING HABITS AMONG TWO STRATA OF CIVILIAN WAR WORKERS. JOHN DOLLARD, Quart. J. Stud. on Alcohol **3**:236 (Sept.) 1942.

Dollard presents data concerning drinking habits among two strata of civilian war workers. The studies were carried out on migrant clerical and secretarial workers in Washington, D. C., and on skilled and unskilled migrant workers in war plants in Bridgeport, Conn. An increase of drinking was noted, probably due to a large extent to the migrant situation itself and the increase in earnings.

The Washington group seemed to do more drinking than did the Bridgeport group. Members of the latter group who had recreational or social problems or were dissatisfied with working conditions drank more than they did at home. It was also observed that those who earned more money drank more than before the war. A larger proportion of those who worked on the day shift drank more than those who worked on the evening or the night shift. Married men separated from their families, like single men, appeared to drink more.

In Washington, D. C., a significantly larger proportion of men than women spontaneously mentioned drinking as one of the things they did when they went out with their friends.

LESKO, Bridgeport, Conn.

THE ALCOHOL PROBLEM IN MILITARY SERVICE. MERRILL MOORE, Quart. J. Stud. on Alcohol **3**:244 (Sept.) 1942.

Moore discusses the problem of alcoholism in military service. He believes it is essentially an emotional or a personality problem, just as it is in civilian life, though it is also directly related to the release of unspent energy in recreations and diversions. He asserts that 95 per cent of the men who drink too much while on leave would accept nonalcoholic entertainment just as readily, and he suggests that alcoholic entertainment in moderation in a wholesome setting should be encouraged and emphasized. Facilities for recreation and relaxation should

be provided for men in the service. The most important factor, he says, is to discover and understand the type of individual who drinks to excess and to keep him out of the armed forces.

LESKO, Bridgeport, Conn.

Diseases of the Brain

THE RELATION OF NEUROTROPIC STREPTOCOCCI TO ENCEPHALITIS AND ENCEPHALITIC VIRUS. E. C. ROSENOW, Proc. Staff Meet., Mayo Clin. **17**:551 (Nov. 4) 1942.

Rosenow has reported consistent isolation of a neurotropic type of streptococcus in epidemic encephalitis, epizootic encephalitis in the fox and equine encephalomyelitis. This type of streptococcus was isolated from fifty-five emulsions made from the brains of human beings, horses, sheep, a hog, a dog, a mink, a bat, chickens, wild ducks, a goose, a pheasant and fish that had died of encephalitis during the studies on the epidemic of encephalitis in North Dakota and Minnesota in 1941. The streptococcus was demonstrated in material obtained from nature, such as mosquitoes and flies; indoor and outdoor air; dust from air-conditioning filters; water from first rains, lakes, rivers and streams, and soil from the bottom of a lake where deep-feeding ducks were dying. These materials and old chick embryo cultures of these materials which contained the streptococcus were inoculated into guinea pigs and mice. Thirty-nine specimens were inoculated into 174 guinea pigs and 236 mice; 53 per cent of the guinea pigs and 40 per cent of the mice died of encephalitis. "The parallelism of isolation of this type of streptococcus from, and the occurrence of encephalitis after inoculation of, diverse materials including washings from outdoor air, was so striking and constant as to suggest a relation between the streptococcus and the 'virus' and that the inciting agent of the epidemic, which occurred over such a vast area, was air borne. Accordingly, experiments were performed to test these ideas a step further."

"Pure cultures of forty-three different strains of the streptococcus, and filtrates of old chick embryo cultures of the streptococcus, far removed from original source and representing dilution of original material of never less than 10-20, were inoculated intracerebrally, intralingually or both intracerebrally and intralingually . . . into 126 guinea pigs and 307 mice. Forty-four per cent of the guinea pigs and 50 per cent of the mice [died of] encephalitis. Similar results were obtained in Rhesus monkeys.

"The virus was found in the brain of animals that had died of encephalitis after inoculation of emulsions from brain tissue (1) of animals and fowl that had succumbed to spontaneous encephalitis, (2) of animals that died of encephalitis after inoculation of material from nature and (3) of animals that succumbed after injection of virus derived from the streptococcus; this virus produced encephalitis consistently in guinea-pigs and mice in from three to seven or more passages. The streptococcus was isolated after the first or second passage of the three types of material from the brains of animals that had succumbed to encephalitis as follows: from eighty (40 per cent) of 198 brains of guinea-pigs cultured, from 163 (36 per cent) of 450 brains of mice cultured, and from the brains of animals that succumbed to successive passages of the virus. Eighty-nine guinea-pigs and 243 mice remained well after inoculation of forty-seven control emulsions and filtrates of emulsions of the brain of normal guinea-pigs and mice or sterile chick embryo mediums. Cultures from the brains of forty-three guinea-pigs and 107 mice, 150 animals, that remained well and that were killed revealed streptococcus in only two instances. From these experiments it was concluded that the streptococcus which we have isolated so consistently was a probable source of virus."

Rosenow attempted to determine whether the streptococcus would invade the brains of animals caused to breathe, and perhaps to swallow, the streptococcus and, if so, whether the virus could be produced in this way. Pure cultures of streptococcus far removed from original source were nebulized into the air of cages in which mice were kept and were added to running water in which fish were kept. Encephalitis was produced in mice by this means. Moreover, emulsions or filtrates of emulsions of the brains of mice which died of encephalitis, when inoculated through three additional passages in mice, produced encephalitis in significant numbers in the three passages.

Similar experiments were carried out on fish. Emulsions or filtrates of emulsions of the brains of 6 fish, representative of a group dying in large numbers in 1941 during the encephalitis epidemic, produced encephalitis in 11 of 27 guinea pigs and in 22 of 38 mice after intracerebral and intralingual inoculation. Further experiments tended to show that the transmission of the streptococcus was by respiration or ingestion of the streptococcus contained in the water.

"Sections of the brains of the fish that died late after exposure to the streptococcus revealed lesions of encephalitis, as did sections of the brains of guinea-pigs and mice that

were inoculated with emulsions or filtrates of emulsions of the brains of fish and mice that were caused to respire the streptococcus. The lesions became more typical as the virus was passed successively through guinea-pigs and mice. Diplococci similar to those found in sections of the brain in studies of epidemic encephalitis in human beings were found in the lesions of some of the animals that died from spontaneous encephalitis and in the lesions of guinea-pigs and mice that succumbed to encephalitis after inoculation of virus strains obtained from nature and from experimental animals. A virus phase of the streptococcus appeared to have developed in the mice and fish that were made to respire and perhaps swallow the streptococcus."

Rosenow concludes from his experiments that (1) the streptococcus is a source of what is now considered virus, (2) that virus represents the filtrable phase of the streptococcus and (3) that spread of the streptococcus by air was a major factor in causing encephalitis to occur in epidemic proportion over such a vast area in 1941. ALPERS, Philadelphia.

METASTATIC BRAIN ABSCESS. ROBERT W. BUXTON and M. L. WHITE JR., Surgery 13:309, 1943.

In 6 of a series of 132 cases of chronic nontuberculous empyema metastatic abscess of the brain was present, an incidence of 4.5 per cent. In all cases in which the empyema was classified as chronic the known duration was three months or more. In only 1 of the 6 cases was the pulmonary tissue underlying the pleural space free from suppuration. In 4 cases no residual empyema cavity existed at the time of death. Of 72 cases of metastatic abscess of the brain collected from the literature, the cerebral complication arose from an intrinsic pulmonary suppurative process in 82 per cent and was attributed to empyema in 18 per cent. In the authors' cases the cerebral condition ran an acute course, in 4 cases the period from the onset of cerebral symptoms to death being five to ten days. None of the abscesses were encapsulated; in 4 cases the lesion was solitary, in 1 case multiple and in 1 case multilocular. In 2 cases the abscess ruptured into the ventricles, and in all cases purulent meningitis was present. No definite correlation was noted between manipulation at the site of drainage of the empyema cavity and the onset of cerebral symptoms. In 2 cases the cerebral abscess was drained surgically, and in 1 the abscess was evacuated through the exploring needle. In these 3 cases appropriate chemotherapy with sulfonamide compounds was carried out, but all the patients died. SHENKIN, Philadelphia.

ARTERIAL HYPERTENSION IN RELATION TO HYPOTHALAMOHYPOPHYSIAL SYSTEM. A. VAN BOGAERT and F. VAN BAARLE, Cardiologia 5:275, 1941.

Van Bogaert and van Baarle point out that in some cases of essential hypertension there exist diverse sympathetic signs which resemble those produced by experimental stimulation of the hypothalamus in dogs. The authors explored the possible role of hypophysial hyperactivity or of normal hypophysial secretion on the stimulation of the hypothalamic centers and tracts. As a result of a critical study of signs of hypophysial hyperactivity in a case of essential hypertension, the authors have arrived at the following conclusions: Liberation of the encephalobulbar sympathetic pressure centers causes, on the one hand, arterial hypertension and, on the other, excessive secretion of the hypophysial hormones. Numerous animal experiments enabled the authors to prove this hypothesis. The presence of hypophysial hormones in larger than normal quantities in the body fluids does not permit the conclusion that a causal connection exists between this hypophysial secretion and the increased blood pressure, since both are independent sequels of an excitation of the sympathetic encephalobulbar centers, among them those of the hypothalamus. J. A. M. A.

SJÖGREN'S SYNDROME: ITS RELATION TO THE PLUMMER-VINSON SYNDROME AND RIBOFLAVIN AVITAMINOSIS. A. FRANCESCHETTI, Confinia neurol. 4:343, 1942.

Sjögren expresses the belief that the filiform keratitis described by Leber in 1882 is not merely an ocular manifestation but part of a general syndrome characterized by extreme dryness of all the mucous membranes. Franceschetti states that there is a resemblance between the syndrome of Sjögren and that of Plummer and Vinson, in which dysphagia is associated with secondary anemia and superficial glossitis. Meulengracht and Bichel noted the close resemblance between the Plummer-Vinson syndrome and ariboflavinosis; as a consequence, Franceschetti postulates that the Sjögren syndrome may present the ocular signs of riboflavin deficiency. The increased sedimentation rate, however, and the frequency of symptoms referable to the joints do not permit the exclusion of an infectious factor. Franceschetti found normal values for vitamin A in patients with Sjögren's syndrome. He treated 2 patients with daily injections containing thiamine hydrochloride, riboflavin, nicotinic acid, pyridoxine and panto-

thenic acid. One of the patients was favorably influenced as far as the condition of the buccal mucous membrane was concerned, but in the other only the rhagades was influenced. The author concludes that although the role of riboflavin in the Plummer-Vinson and Sjögren syndromes is far from clarified, one is justified in pursuing investigation along these lines.

DeJong, Ann Arbor, Mich.

A CASE OF TRAUMATIC NARCOLEPSY. C. J. URECHIA, Confinia neurol. 5:132, 1942.

Urechia reports the case of a man aged 31 who manifested narcolepsy, increased salivation and right hemiparesis after an injury to the skull. He postulates the presence of a lesion in the vicinity of the third ventricle, involving the centers controlling sleep and the vegetative functions.

DeJong, Ann Arbor, Mich.

PARALYTIC SYNDROME DUE TO CANCER OF THE PAROTID. ALFREDO C. MENZANI and JUAN CHIARAVALLE, Rev. neurol. de Buenos Aires 7:254 (July-Sept.) 1942.

Menzani and Chiaravalle describe a case of cancer of the parotid gland with involvement of the lower cranial nerves and call it an instance of "paralytic syndrome of cancer of the parotid gland," a term used by Collet and Bonnet.

A man aged 40 had sudden onset of paralysis of the right side of the face and noticed coincidentally a nodule in the parotid gland on the same side. During the next ten months he lost 22 pounds (10 Kg.). When first seen he had total paralysis of the right side of the face, paralysis of the palate, difficulty in swallowing and dysphonia. At operation an encapsulated tumor, located between the tip of the mastoid and the angle of the maxilla, was removed, with exposure of the facial nerve, which was discolored and flattened. Eight months later the following signs, all on the right side, were present: complete paralysis of the face; total involvement of the vagoglossopharyngeal complex except for taste; paralysis and atrophy of the sternocleidomastoid and trapezius muscles, and atrophy and paralysis of the tongue.

The authors conclude that the involvement of the ninth, tenth, eleventh and twelfth nerves occurred as result of metastasis to the glands of the lateral pharyngeal space, since they were not able to demonstrate sufficient tumor growth to cause direct pressure on these nerves. On the other hand, the facial nerve, as shown at operation, was directly compressed by the neoplasm. They believe that the progressive involvement of the nerves in the manner described is typical of cancer of the parotid gland.

PIETRI, New York.

CEREBRAL LOCALIZATION. RAÚL GARABELLI, Rev. neurol. de Buenos Aires 7:289 (Oct.-Dec.) 1942.

Garabelli reports 2 cases of tumor of the left frontal lobe associated with motor apraxia. The first case was that of a woman aged 50 who was hospitalized because of epileptiform seizures. She showed spatial and temporal disorientation, mental dulness, inattention, slowness of movements, loss of initiative and hesitancy. Soon after admission she began to have jacksonian spells, involving chiefly the right upper extremity and the right side of the face. Careful tests of the movements of the head and extremities showed pure motor apraxia on both sides, more pronounced on the right. It was established that the patient could understand perfectly the orders given. She was observed for five years, during which time the apraxia became gradually worse until it was complete on the right side and nearly so on the left, so that she was unable to walk or in any way to produce useful movements. Strength was retained throughout; no signs of involvement of the pyramidal tract developed.

Autopsy revealed a meningioma, the size of a large orange, which had destroyed totally the first and second frontal convolutions, as well as the supracallosal gyrus, on the left side, at the same time compressing the third frontal gyrus downward. The tumor exerted pressure on the right frontal lobe, the genu of the corpus callosum and the caudate and lenticular nuclei of both sides, especially the left.

The second case was that of a woman aged 37 with a history of character changes and hypersomnia of six and a half years' duration. Five years after the onset of these symptoms she had her first convulsive seizure, and soon thereafter vision became impaired. Papilledema and increased intracranial pressure suggested the presence of a neoplasm. Neurologic examination showed diminished abdominal reflexes on the right side; otherwise, the status was normal except for apraxia.

Again, in this case, the apraxia was more severe on the right side and was most noticeable in the lower extremity, the difficulty being less in the upper extremity. There was no disturbance of speech.

A diagnosis of tumor of the first and second frontal convolutions was made. Autopsy revealed a glioma of the right prefrontal region, which destroyed the first and part of the

second frontal convolution and nearly all the frontopolar white matter. There was invasion of the supracallosal gyrus, the genu of the corpus callosum, the corona radiata and the opposite supracallosal convolution.

The author notes that in both cases the postrolandic region was not involved and the gnosias were intact. The cases add further proof in support of the claims of Jakob (*Semana méd.*, Oct. 31, 1907) that motor apraxias are of frontal lobe origin.   PIETRI, New York.

HEMORRHAGIC MENINGOENCEPHALITIS CAUSED BY EMBOLI OF ACTINOMYCES. JULIO ARANOVICH, Rev. neurol. de Buenos Aires **7**:331 (Oct.-Dec.) 1942.

Aranovich reports a case of invasion of the brain by Actinomyces, unusual because of the embolic character of the lesions. A man aged 42 had been operated on for gastric ulcers at the age of 25 and again at the ages of 40 and 41 years. On Jan. 30, 1941 a fourth operation was performed. The following day, while receiving an infusion of dextrose, he suddenly lost consciousness and became intensely pale. The blood pressure fell, and a febrile state developed. Hemiplegia of the left side appeared soon thereafter, and he died four days later, without further change in symptoms. Postmortem examination was limited to the head. Grossly, the meninges showed marked congestion, with small subarachnoid extravasations of blood in the right frontal and left occipital regions. Perivascular hemorrhages were present in the cortex, especially in the right frontal and the left occipitoparietal area, the head of the left caudate nucleus, the left internal capsule, both thalami and the cerebellum.

Microscopically, the perivascular nature of the hemorrhages was established, and both neuronal and axonal degenerative changes were observed together with proliferative changes in the neuroglia in the older lesions. A large number of the vessels of the white matter were partially or totally occluded by dichotomous filaments and "metachromatic granules," typical of Actinomyces.

Aranovich believes that the infusion of dextrose probably helped to spread an invasion from an unrecognized focus, not established by autopsy but probably of gastrointestinal origin. The presence of older vascular lesions presupposes occasional mild invasions of the blood stream, with the formation of a few scattered emboli on each invasion.

PIETRI, New York.

CEREBELLAR SYNDROME OF MALARIAL ORIGIN. MARIO MENDEZ and NOE HUAMAN, Rev. de neuro-psiquiat. **4**:106 (March) 1941.

A child aged 13 years was stricken by malarial fever, with chills, headache, fever and vomiting. Two months later, he felt dizzy and had difficulty in articulating, and his movements became incoordinate. He was unable to stand or walk without help, although muscular power and sensation were unaffected. There were also dysmetria, dysdiadokokinesis and nystagmus.

Three months after the onset of the illness Plasmodium vivax was found in the blood. With the administration of specific treatment (presumably quinine) the fever was abolished, and there was regression of the cerebellar syndrome during the following fortnight.

DE GUTIÉRREZ-MAHONEY, Coral Gables, Fla.

STRIATAL SYNDROME WITH RHEUMATOID ARTHRITIS AFTER NITROUS OXIDE ANAESTHESIA. A. M. LORENTZ DE HAAS, Acta psychiat. et neurol. **16**:405, 1941.

De Haas reports the history of a man aged 45 who underwent a gastric resection under nitrous oxide anesthesia. He was cyanotic during the anesthesia, and his respiration suggested lack of oxygen. There was arrest of breathing for two or three minutes. Artificial respiration and cardiac massage brought about first arterial pulsation, followed by the return of respiratory movements. The cessation of respiration must have increased the cerebral anoxemia. Chronic hypoxemia was probably the main cause of the development of a typical striatal syndrome and mild signs of a lesion of the pyramidal tract. The report is presented chiefly because the patient, who had never had articular complaints, five weeks after the operation manifested pain, redness and swelling of various joints of the arms and legs. The rheumatoid arthritis was associated with fever. It has been suggested that a connection exists between lesions of the corpus striatum (or substantia nigra), as observed in cases of paralysis agitans, and conditions similar to osteoarthrosis and chronic rheumatoid arthritis. Some investigators consider that all abnormalities of joints falling within the scope of rheumatism (including therefore rheumatic fever and acute rheumatoid arthritis) are primarily determined cerebrally. The case presented here may be of some significance in this connection. As far as the author knows, no such case has been reported before.

J. A. M. A.

DUPUYTREN'S CONTRACTURE AND EPILEPSY: CLINICAL CONNECTION BETWEEN DUPUYTREN'S CONTRACTURE, FIBROMA PLANTAE, PERIARTHROSIS HUMERI, HELODERMIA, INDURATIO PENIS PLASTICA AND EPILEPSY, WITH ATTEMPT AT A PATHOGENIC EVALUATION. M. LUND, Acta psychiat. et neurol. 16:465, 1941.

Lund has not been able to find in the literature any attempt to correlate Dupuytren's contracture with epilepsy. His own observations at an institute for epileptic patients demonstrate that the two diseases concur sufficiently often to suggest a pathogenic relationship. The literature on pathogenesis of Dupuytren's contracture emphasizes the hereditary factor, chronic trauma, a neurotrophic disturbance and, finally, a fibroblastic diathesis, a tendency to mesenchymal hyperplasia. Dupuytren's contracture may manifest itself as simple nodular thickening of the palmar fascia or may be associated with the characteristic puckering of the skin; there may be active or passive contracture of the fingers. The author had examined 190 male and 171 female patients with epilepsy for the presence of Dupuytren's contracture, fibroma plantae and periarthrosis humeri. Of the males, 22.6 per cent had nodules or thickened bands in the palmar fascia, 15.8 per cent had the characteristic puckering of the skin in the palm and 11.6 per cent had contracture of the fingers. The percentages among the epileptic females were about half as high. Fibroma plantae was found in 13 males and 12 females; 22 of these had also Dupuytren's contracture. Twelve patients had periarthrosis humeri, 11 of whom had Dupuytren's contracture as well. Of 100 males and 100 females examined for "heloderma" (subcutaneous fibroma of the dorsal aspect of the middle joints of the fingers), the condition was found in 29 males and 13 females; 29 had Dupuytren's contracture, as well as heloderma. Of 100 males examined for induratio penis plastica, the lesion was found in 3 patients; 2 of these had also Dupuytren's contracture. Comparison with a control group consisting of 1,021 workers doing hard manual labor showed that Dupuytren's contracture was four times as frequent among the epileptic patients as among the workers; the degree of the contracture seemed to be more pronounced and the age of manifestation lower among the epileptic patients. Among the workers there was only 1 with fibroma plantae (0.1 per cent); among male epileptic patients, there were 13 (6.8 per cent). Heloderma was about twenty times as frequent among the epileptic patients as among the controls. Future investigations should concern hereditary connections between epilepsy and fibroplastic diathesis, the possibility that these disorders are due to functional disturbances in the vasomotor system in epileptic patients (constant hypersympathectomy?) and the question whether prolonged treatment with phenobarbital could be responsible.

J. A. M. A.

GASTROINTESTINAL SYMPTOMS IN TUMORS OF BRAIN. H. E. NIELSEN, Ugesk. f. læger 103:1530 (Nov. 27) 1941.

Nielsen found that in 8 out of 25 cases of verified tumor of the brain gastrointestinal symptoms were the first signs of the cerebral disorder and dominated the picture until the diagnosis of brain tumor was made. He divides the cases into those of dyspepsia, in which the symptoms are more indefinite, and those of ulcer, in which the symptoms of ulcer are more or less well defined. The gastrointestinal symptoms do not afford an indication of the localization of the cerebral tumor, although most of the tumors had a near relation to the fourth ventricle. With respect to the relation between gastrointestinal ulcer and tumor of the brain, the importance of the neurogenic factor in pathogenesis of ulcer in general is emphasized.

J. A. M. A.

Muscular System

SUBCAPSULAR CATARACTS IN DYSTONIA MUSCULORUM DEFORMANS. EUGENE ZISKIND and RAPHAEL KOFF, Bull. Los Angeles Neurol. Soc. 7:204 (Dec.) 1942.

Ziskind and Koff report a case of dystonia musculorum deformans with polar cataracts. The interesting feature of the case is the presence of polar cataracts in a patient with a neuromuscular disorder other than myotonia atrophica.

LESKO, Bridgeport, Conn.

THE EFFECT OF VITAMIN E ON THE MUSCULAR DYSTROPHIES. BERNARD J. ALPERS, HERBERT S. GASKILL and A. CANTAROW, J. Nerv. & Ment. Dis. 95:384 (Oct.) 1942.

Alpers, Gaskill and Cantarow studied the creatine-creatinine excretion and the clinical features of 6 patients with progressive muscular dystrophy who had been treated with preparations of vitamin E for from six to twenty-three months. Each patient was studied in the hospital while receiving a weighed diet containing a constant amount of protein, and the

daily urinary output of creatine and creatinine was measured before and during periods of vitamin E therapy. It was found that the daily levels of creatine-creatinine excretion were not altered by the therapeutic measures, and in no instance was the creatine excretion consistently diminished or the creatinine output increased. Five patients showed no clinical improvement, and 1 showed definite progress of the disease. No additional effect was noted when vitamin B complex was added.

CHODOFF, Langley Field, Va.

STREPTOCOCCAL INFECTION OF MUSCLE. J. D. MACLENNAN, Lancet **1**:582 (May 8) 1943.

MacLennan presents a series of 8 cases of war wounds involving the limbs encountered in the Middle East during the present war. The cases were clinically similar in the presentation of erythema of the affected part, a greater or less degree of foul odor, at least a trace of gas and edema, of varying degree, of both the skin and the underlying muscle. The bacteriologic diagnosis was made on the basis of the presence of hemolytic streptococci in all cases. No clostridia were seen. Anaerobic streptococci were present also in 4 of the 8 cases. Sections of muscle showed that the streptococci outnumbered by far all other organisms present.

The author points out that the condition differs clinically from gas gangrene in that the odor is neither so foul nor so pungent as that of true gas gangrene and the muscle is alive and reacts to stimuli and has none of the boiled, coagulated appearance of tissue infected with anaerobic spore-bearing organisms. The skin is more involved in streptococcic than in clostridial infections. Outstanding is the presence of great numbers of streptococci in muscle smears.

In 6 cases conservative treatment with oral and local administration of sulfonamide compounds was carried out, with recovery in all instances. In 2 cases amputation was done before the correct diagnosis was made; 1 of the patients died, and the other recovered.

McCARTER, Philadelphia.

MYOTONIA CONGENITA ATROPHICA: STUDY OF A FAMILY. F. QUIROS M. and E. GARCIA CARRILLO, Rev. mex. de psiquiat. **9**:15, 1942.

This is a study of the only family with myotonia to be reported from Costa Rica. Endocrine disturbances were frequent, as well as alopecia and cataract. The mother of the present family was myotonic. The maternal grandfather was not myotonic but had cataracts. In the present family 3 men, aged 26, 28 and 30, are myotonic. One woman is married and sterile and suffers from urticaria and Quincke's edema but is not myotonic. One brother was born dead. The authors insist on the variations in the pathologic picture, especially the anomalies of the electrocardiogram.

BAILEY, Chicago.

POSTINFECTIOUS MYASTHENIC SYNDROME. JORGE V. BERNALES and A. BORDA, Rev. de neuropsiquiat. **4**:113 (March) 1941.

A man aged 30 had a dental abscess in 1928, and four days later he noted drooping of the right eyelid, double vision and drowsiness. Quinine accentuated his symptoms, and hypotonia of the facial musculature and paresis of the right arm and leg developed. He was treated for the infection, which had existed for three months, and one month later his disabilities disappeared, so that he was able to take exercise. In 1930 he received a gunshot wound in the upper portion of the right arm, which left him with partial palsy in the distribution of the radial nerve. For the following ten years he was able to carry on his work, which demanded considerable vigor, but early in 1941 he began to feel fatigue out of proportion to his efforts. There was greater difficulty of extension of the fingers of the left hand; the right eyelid drooped, and he saw double. The symptoms resembled those of twelve years before, and they became worse, with impairment of muscular power, especially of the right arm and leg, so that he had difficulty in walking. The left eyelid drooped, and a fixed facial expression developed. Speech became weak after a few hours of conversation. He could chew and swallow the first mouthfuls of food fairly well and later ones with difficulty. Intramuscular injection of 2 cc. of prostigmine methylsulfate and 0.25 mg. of atropine sulfate improved his condition within ten minutes; the improvement was maintained for six hours after each injection. Mucopurulent nasopharyngitis and six dental abscesses developed. The teeth were removed.

In retrospect, it was difficult to state whether the symptoms were myasthenic components of such a disease as lethargic encephalitis. Actually, the patient had myasthenia, with accentuation of his symptoms in the muscular territories which were then paretic. It was not possible to demonstrate hypertrophy of the thymus or any constitutional factors which

could be considered responsible; so all diagnostic discussion was limited to the infections considered as etiologic factors in myasthenia. Although in some cases of myasthenia there are obvious causal relations with lethargic encephalitis, in this case there was no manifestation of an encephalitic infection of the virus of the von Economo type. This negative evidence strengthened the impression that the numerous foci of infection of the mouth constituted, in this case, the most likely cause of the myasthenic condition.

DE GUTIÉRREZ-MAHONEY, Coral Gables, Fla.

Encephalography, Ventriculography, Roentgenography

SYNDROME OF AMYOTROPHIC LATERAL SCLEROSIS OF BULBAR TYPE ASSOCIATED WITH PLATY-BASIA. RICHARD H. YOUNG, J. Nerv. & Ment. Dis. **97**:133 (Feb.) 1943.

In the recent literature on platybasia such neurologic conditions as syringomyelia, disseminated sclerosis, spastic paralysis, hydrocephalus and involvement of bulbar and cerebellar mechanisms and of the lower cranial nerves have been reported to occur in association with the anomaly. Young reports 2 cases with a clinical picture of bulbar amyotrophic lateral sclerosis and roentgenographic evidence of platybasia. Prominent symptoms in both cases were early occipital pain, pain on turning the head from side to side, weakness and numbness of the extremities, signs of bulbar involvement and cerebellar symptoms; in 1 case lumbar puncture revealed partial subarachnoid block. The author concludes that roentgenographic examination of the base of the skull and the upper cervical portion of the spine is warranted in cases in which the syndrome of amyotrophic lateral sclerosis is presented.

CHODOFF, Langley Field, Va.

CONGENITAL NARROWING OF THE LUMBOSACRAL SPACE. THEODORE H. VINKE and EDGAR H. WHITE, Surg., Gynec. & Obst. **76**:551, 1943.

Narrowing of the lumbosacral intervertebral space, as seen in roentgenograms, has recently been interpreted as the result usually of herniation of the nucleus pulposus. Vinke and White believe that congenital narrowing of the disk in this interspace occurs more frequently than is commonly supposed. The roentgenograms of 300 children between the ages of 5 and 15 years were reviewed, none of the children being included in the study for whom there was evidence of fracture, infection or trauma or whose roentgenograms were unsatisfactory. Any narrowing of the interspace in this series must, they felt, be of congenital origin. Three cases of this anomaly were found, the narrowing in all being associated with lumbarization or sacralization. Other observers had previously noted associated narrowing of the interspace with congenital anomalies of the lower part of the back, particularly sacralization. The cases of 6 adults with pain in the lower part of the back, without sciatica and with appreciably narrowed lumbosacral interspace, are reported. In these 6 patients none of the signs suggested ruptured intervertebral disk. All responded excellently to conservative management.

The authors conclude that in questionable cases of herniated disk a narrowed lumbosacral interspace should invite close observation for other congenital anomalies before it is used as supportive evidence in favor of a herniated disk.   SHENKIN, Philadelphia.

Society Transactions

CHICAGO NEUROLOGICAL SOCIETY

ARTHUR WEIL, M.D., *President, in the Chair*

Regular Meeting, March 18, 1943

Landry's Paralysis: Its Clinical and Pathologic Features. DR. GEORGE B. HASSIN.

It is well known that the condition which Landry described in 1859 as an acute ascending paralysis is not a morbid entity but a symptom complex. It may occur in a number of diseases of the spinal cord, the peripheral nerves and the brain itself. It is noteworthy that the muscles have not been considered as a possible pathologic substratum of this syndrome. Through Dr. Victor Levine, pathologist to the Municipal Contagious Disease Hospital, Chicago, I had the opportunity to study the condition of the musculature in a case of acute anterior poliomyelitis (Heine-Medin disease) in which the clinical picture of Landry's paralysis was exhibited. The patient, a boy aged 12 years, died forty-eight hours after development of flaccid paralysis, first, of the lower and, later, of the upper extremities, followed by partial paralysis of the oculomotor nerves, difficulties in respiration and speech and death.

Necropsy, performed by Dr. Levine, revealed disseminated foci of inflammation in the spinal cord, brain, cerebellum and pons, combined with destruction of the ganglion cells in the spinal cord. Dr. Levine supplied me with material from several muscles (the psoas, abdominal and intercostal muscles, the diaphragm and the pectoralis major and minor). Some of these muscles (the psoas and abdominal muscles) presented no changes. Others (the pectoralis muscles, the diaphragm and the intercostal muscles) exhibited pronounced changes. The muscle fibers were swollen, devoid of longitudinal and transverse striations, homogeneous and occasionally waxlike and broken up into fibrils; the endomysium and the perimysium were infiltrated with cellular elements, chiefly fibroblasts mixed with lymphocytes. The changes which were especially noticeable in the muscles of the heart were both parenchymatous and inflammatory. They were analogous to what is associated with some forms of polyneuritis and, for want of a better name, may be termed peracute polymyositis. The involvement of the musculature may be responsible for such clinical manifestations as the rapid course of the disease, respiratory difficulties and sudden death. The muscular changes may also explain those paradoxic cases, by no means rare, in which no anatomic changes could be demonstrated in the nervous system and the clinical picture was one of an organic nervous disorder. It follows that in every case in which there is a clinical picture of Landry's paralysis the muscles, and a large number of them, should be carefully studied for the purpose of establishing whether changes are present and whether they alone may not be the cause of the paralysis.

DISCUSSION

DR. HERMAN JOSEPHY, Lincoln, Ill.: I should like to ask Dr. Hassin whether he thinks that this pathologic condition of the muscles is typical of all cases of Landry's paralysis or whether this case is an exception. It is difficult to understand how a disease of the skeletal muscles could result in such a systematic ascending paralysis as that seen in Landry's syndrome. The typical clinical course is more easily understood as a consequence of degeneration or inflammation of the spinal cord, which progresses continuously from below upward.

DR. REUBEN STRONG: The appearance of striations in sections of normal skeletal muscle is variable; sometimes they are scarcely to be seen at all. On the other hand, in muscle taken from the cadaver fixed only in embalming fluid, good striations are apparent. Will Dr. Hassin describe the orientation of the section which showed muscle fibers cut obliquely? I do not consider this fair material for comparison with the section in which the muscle fibers were cut longitudinally. Furthermore, some of the difference might be due to faulty fixation.

DR. MABEL G. MASTEN, Madison, Wis.: As pointed out by Dr. Hassin, Landry's paralysis has developed into a syndrome characterized by rapid development of ascending motor paralysis with insignificant changes in the central nervous system. Cannot something be done to clarify the confusion which exists in clinical differentiation? The term is now used to designate any fulminating ascending paralysis.

There is reason to believe that in Landry's original case the picture may have been quite different from that now labeled Landry's paralysis. Dr. Madelaine Brown and Dr. George C. Shattuck, independently translated Landry's original report and arrived at the same conclusion—that the disease in his case was the result of nutritional deficiency (beriberi).

In entire agreement with Dr. Hassin that changes in the muscles in this disorder have been overlooked, I wish to point out that similar muscular changes may be observed in other clinical disorders with a pathologic process in the peripheral nerves as well as in the central nervous system. The changes in the muscles associated with polyneuritis, no matter what the etiologic agent—arsenic, alcohol or food deficiency—are similar to those demonstrated by Dr. Hassin in this report and to those accompanying known deficiencies, such as beriberi.

My conviction that the muscles played a role in the paralysis and the painful state of the muscles led several years ago to my making biopsies in a number of cases of polyneuritis, with the observation in all instances of changes in muscles, and in many instances in blood vessels, similar to those in Dr. Hassin's case. The disorder known as the Guillain-Barré syndrome, or "infectious neuronitis," sometimes appears as a rapidly developing ascending motor paralysis, to be differentiated as an entity only by the presence of a high protein content of the spinal fluid and albuminocytologic dissociation. The recovery of function in many cases of this syndrome is so rapid and complete that it seems that changes in the nervous system cannot entirely account for the degree of paralysis—that changes in the muscle must contribute a part.

It is hoped that Dr. Hassin's report will stimulate more extensive studies of muscle in cases of Landry's paralysis, as well as of polyneuritis and infectious neuronitis.

Dr. Ben W. Lichtenstein: The general pathologist has always insisted on the differentiation of organic pathology and the pathology of disease. In lobar pneumonia, for example, there is a pathologic process in the lungs, but autopsy reveals lesions in other parts of the body as well. Although typhoid is characterized by lesions in the intestine, I have performed autopsy in cases in which no alterations were observed in the intestine, but changes were conspicuous in the myocardium, the liver and the spleen.

Poliomyelitis is regarded as a disease in which the essential pathologic process occurs in the central nervous system. All know, however, that, as in typhoid and other infectious diseases, pathologic changes may be observed in other structures of the body as well. In many cases of infantile paralysis the myocardium shows profound inflammatory changes. I look on the changes Dr. Hassin demonstrated in the muscles in his case of acute anterior poliomyelitis as an associated pathologic process. Such associated lesions are manifestations of the disease and may in some instances color the clinical picture.

Dr. Peter Bassoe: Dr. Hassin has done a service in calling attention to changes in the muscles, but I should like to know whether acute ascending paralysis can conceivably be produced by changes in the muscles only. So far as I know, acute polymyositis is not ascending. I should like to know, also, whether he knows of any case in which thorough study of the nerve roots and peripheral nerve endings revealed no changes in the peripheral nerves or in the spinal cord.

One must accept Dr. Hassin's description of muscular degeneration in these cases, but I am suspicious of the hourglass constrictions and other narrowings of the fibers. They remind me of old descriptions of "segmentation and fragmentation of the myocardium" and of certain "heterotopias" of the spinal cord—all artefacts.

Dr. George B. Hassin: I do not know how involvement of the muscles can explain the segmental spread in Landry's paralysis. The paralysis may be not only ascending but descending and may even begin with the bulbar nerves. The point is whether involvement of the musculature alone may give a clinical picture of Landry's paralysis. The muscular changes here demonstrated are not artefacts, nor are they the result of improper sectioning or handling of the tissues and sections. The material was furnished by Dr. Victor Levine, who knows how to handle pathologic material. Some of the muscles he sent me showed no changes whatever; others, handled in the same manner, exhibited prominent changes in both the parenchyma and the mesodermal tissue. The conspicuous infiltrations in the latter certainly were not artefacts.

I did not get the impression from a careful reading of Landry's paper that the condition described was due to a vitamin deficiency. An enormous literature has come into existence since Landry's publication, in 1859, but, in my opinion, his description of the disease is still the best. Polyneuritis of any type, including neuronitis, as described by Kennedy, Casamajor and Bradford, and the radiculoneuritic type of· Guillain and Barré, may give a clinical picture of ascending paralysis. Some time ago, largely under the influence of Leyden's followers, polyneuritis was said to be the essential cause of Landry's paralysis. Krewer, for instance, plainly stated that polyneuritis is a condition *sine qua non* of Landry's paralysis. Such teaching was replaced by an even more popular theory, that poliomyelitis is the anatomic cause of ascending paralysis. However, in many instances neither the peripheral nerves nor the spinal cord nor any other portions of the nervous system—

roots, ganglia, sympathetic nervous system or brain—exhibit changes that can explain such an ominous clinical picture as a rapidly spreading paralysis involving the extremities, the trunk and the bulbar nerves. It is hard to conceive that such a morbid condition should lack a pathologic foundation.

Dr. Lichtenstein's comments are appropriate. The late Dr. LeCount frequently spoke of the importance of combining a pathologic study of the nervous system with that of the organs and the body in general. Also of great importance is Dr. Bassoe's reference to polymyositis. This is a rare condition. I have never seen a case of polymyositis, and some textbooks (those of Gowers, Mettler and Grinker) do not even mention this morbid entity, but Oppenheim and Strümpell, and especially Knoblauch, have given excellent clinical and pathologic descriptions. The form of polymyositis I outlined differs from the types seen in trichinosis, either the septic or the traumatic form, but the question does not concern the name. The point is that in cases of Landry's paralysis in which no histologic changes are demonstrable such lesions should be looked for in the muscles.

Incidence and Significance of Convulsive Disorders in Mentally Deficient Persons. Dr. R. W. WAGGONER and Dr. J. G. SHEPS, Ann Arbor, Mich.

The problem of convulsive disorders in the feebleminded is the most important one in the care of such patients. In 10 per cent of these patients seizures are the cause of death. It was our purpose in this study to investigate incidence of convulsive disorders in feebleminded patients and to determine the relation of convulsions and mental retardation. A series of 254 patients whose condition was verified at autopsy were studied; of these, 105, or 41.3 per cent, had convulsions. Pathoanatomically, the diagnosis was either meningoencephalitis or malformation of the brain. In this material there was no apparent correlation between the incidence of convulsive disorders and either the degree of feeblemindedness or the type of the pathologic process in the brain.

Material showing the different types of neuropathologic lesions in this series was demonstrated.

DISCUSSION

Dr. HERMAN JOSEPHY, Lincoln, Ill.: I cannot give definite figures as to the incidence of epilepsy among the inmates of Lincoln State School and Colony, but I think the percentage among the patients with the lower grades of intelligence is about the same as that given by the authors; among patients with the higher levels of intelligence the percentage seems to be lower than theirs. The incidence depends, of course, to some degree on the type of patient committed by the courts. I agree that it is impossible to draw conclusions as to the mental state of the patient from the pathologic changes in the brain. All kinds of abnormalities of the brain have been encountered in persons who did not show any sign of mental deficiency during life. That is true even for pronounced microcephaly and the typical lesions of tuberous sclerosis.

I should like to discuss the differentiation of endogenous and exogenous feeblemindedness. Usually malformations of the brain are considered endogenous; Tredgold, for example, so classified them. But many experiments have proved that typical malformations may be the result of environmental influences. Whether malformation or disease of the brain and of other organs is endogenous or exogenous can be proved only on the basis of its occurrence in accordance with the laws of heredity, not of anatomic changes.

Dr. A. J. ARIEFF: Among the authors' patients with exogenous feeblemindedness the incidence of epilepsy was 50 per cent, and among the patients with the endogenous form the incidence was 39 per cent. In the study by the late Dr. Paskind and, more recently, in that of Yacorzynski and myself, on deterioration in patients with epilepsy, it was found that only 5 per cent of patients with idiopathic epilepsy, but 37 to 38 per cent of the patients with organic disease of the brain, showed deterioration. The presence of deterioration in an epileptic patient suggests that a developing organic process, and not drugs or the epilepsy itself, is the responsible factor.

Dr. RALPH HAMILL: What percentage of these feebleminded patients had petit mal attacks? My work with children has suggested that the petit mal attack comes close to being a mental phenomena. Many of the children have ceased to have attacks after I have worked with them a short time. One does not see the petit mal attack in adults as often as in children. The authors' figures seem to indicate that there was no essential relation between mentality and convulsive attacks.

Dr. RAYMOND W. WAGGONER, Ann Arbor, Mich.: You will note we divided these patients into those with the endogenous and those with the exogenous form of feeble-

mindedness; under the first head were considered primarily the patients with cerebral mal-
formations, and we assume that these include the greater number. There may be some
cases in which the defect might be called a pseudomalformation—cases in which pathologic
changes may appear superficially to be malformations but are actually due to exogenous
causes. We have considered that some apparent endogenous malformations are the result
of an inflammatory lesion; thus, one must be careful in saying that this condition is a
malformation and that one is not.

Two years ago, in Richmond, Va., we presented a paper which emphasized one of the
points mentioned here—two brains may look almost alike, and yet one patient may have had
attacks and the other not; so there must be something besides the cerebral pathologic
process itself to account for the convulsions.

We pointed out that this study represents a cross section of such patients, not simply
institutional ones; institutional patients are those who cannot be cared for outside the hos-
pital. The percentage ratio for the latter therefore, would differ from that for both types
of patients, such as were considered in this series. It is generally true, although not invariably
so, that the greater the degree of damage to the brain, the greater the degree of mental defect.
No attempt was made to determine the percentage of petit mal attacks in this series.

Alterations in the Central Nervous System Following Experimental Asphyxia at Birth. DR. WILLIAM F. WINDLE.

Experiments were conducted on guinea pigs at term to determine whether asphyxiation
of the fetus by interference with its blood supply produces permanent structural changes in
the central nervous system. The abdomen of the pregnant animal was opened while the
pig was under procaine hydrochloride (1 per cent solution); no other anesthetic was employed.
One fetus was delivered immediately as a control. The uterine blood vessels were then
occluded, and the remaining fetuses were delivered only after cessation of intrauterine respira-
tory movements induced by the anoxia. After nine to twenty-one minutes of asphyxiation
the animals were resuscitated by gentle intermittent inflation of their lungs with oxygen or
with a mixture of oxygen and 10 per cent carbon dioxide. The average time required to
bring about restoration of respiratory reflexes was twenty-nine minutes.

In the early hours after resuscitation animals exhibited spastic decerebrate states, running
movements, tics, convulsions and tremors. Later they righted themselves with difficulty,
falling or rolling to one side. They were hyperirritable and often cried continually. Inco-
ordination, ataxia and spastic gait were observed in some animals for several days. During
this time most animals were somnolent, and certain reflexes, e. g., the startle reaction, were
depressed. Long-standing alterations in behavior are thought to have been observed, but
further study is necessary.

A closely graded series of brains from 30 animals and their litter mate controls were
preserved in dilute solution of formaldehyde U. S. P. (1:10) forty-five minutes to thirteen
weeks after asphyxiation. Every tenth serial section was stained with cresyl violet or
thionine. Control and experimental material were prepared together to facilitate comparison.

Hemorrhages, mainly of the capillary type, were noted in many regions of the brains in
14 of the 18 animals 10 days old or less. In older specimens it was difficult to detect
remnants of hemorrhage. Cerebral edema occurred between the ages of 3 hours and 5 days.

Cytologic changes were observed as early as one to two hours after asphyxiation and
consisted at first of swelling of the nerve cells and dispersion of the Nissl bodies. In three
to four hours vacuolation of the cell cytoplasm, retraction and staining of dendrites and
shrinkage of some cell bodies appeared. These processes continued for several days. At
thirty hours many neurons failed to stain, and at two days typical chromatolysis was
encountered. The process of recovery began at four or five days but was incomplete at
ten days.

Proliferation of glia cells, especially microglia cells, began at the age of 62 hours and
was conspicuous at 10 days of age, and glial plaques were seen at 23 days of age.

Loss of cells was detected at the age of 4 days, when "ghost" forms appeared. It was
pronounced at 8 to 10 days of age and thereafter resulted in atrophy of smaller or larger
regions of the brain. Generalized atrophy was accompanied by enlargement of the ventricles.
Thickening of the pia was noted. Areas of partial softening were seen.

Hemorrhages and/or cytologic changes or loss of cells were encountered in all 29
specimens fixed an hour or more after asphyxiation. Only the animal living less than an
hour showed no pathologic change. None of the control animals exhibited such changes.
Of the asphyxiated pigs, all parts of the nervous system were affected in one animal or
another. There was not the specificity in respect to damage by anoxia at birth that has
been reported for adult organisms, but the cerebellum was less affected and appeared to

recover more completely than other parts. When the cerebral cortex was damaged, all layers appeared to be involved, but the loss of pyramidal cells was most striking. The amount of destruction and the region involved varied greatly from specimen to specimen.

It may be concluded that asphyxiation of the guinea pig during birth results in permanent, although highly variable, structural alteration in the central nervous system. It is suggested that similar results of asphyxia neonatorum occur in man.

DISCUSSION

Dr. R. F. Becker: The animal which has been asphyxiated differs behaviorally in several respects from the control animal. The major differences may be classified briefly as (1) reduced activity; (2) docility; (3) disturbances in feeding behavior, and (4) stereotyped behavior and other differences in learning ability.

The control animal, like all normal guinea pigs, is extremely irritable. It startles readily to loud sounds and rapid movements in its environment. When so disturbed it tends either to "freeze" or to scurry for shelter. It is awake for long periods, busy nursing or even nibbling solid food a few days after birth. It is gregarious, following the mother or the other young about the cage.

The experimental animal is much less active. During the first three or four days it sits apart from the rest, being somnolent most of the time. Many of these animals present a peculiar hunched sitting posture, with the forefeet drawn back close to the hindfeet. The normal animal at rest lies crouched with a perfectly straight back and with considerable distance between the hindlegs and the forelegs. The experimental animal does not startle or scurry to loud sounds or other danger signals; in fact, it pays little attention to its immediate surroundings. We have no objective data on the amount of reduction in spontaneous activity in these animals, but such a study is under way. Usually within a week the experimental animals become much more active, but it is impossible to say yet whether they may not always function at a reduced level of activity.

The experimental animal appears to be more docile; it does not seek to escape capture, but allows itself to be picked up and does not struggle. There is a notable difference in the tenseness of the abdominal musculature. The animal sags limply when picked up by the shoulders, whereas the control animal tenses its abdomen, arches its back and kicks vigorously.

The control animal presents no feeding problem. As soon as it is born it is able to seek out a nipple and to nurse. The experimental animal often has no idea where to seek or what to do when a nipple is presented, and must be fed by dropper. It appears to lack the normal nuzzling reflex. Sometimes it is hypersensitive to touch for the first few days and backs away quickly when touched. Swallowing is often incoordinated, and care must be taken to prevent aspiration into the lungs.

In learning a simple maze or alternation problem the control animal shows considerable variability and plasticity of response. If one pathway is blocked, it readily seeks an alternate course. It becomes cautious before blind alleys in which it has been previously shocked. The learning of the experimental animal runs a stereotyped course. It develops strong positional habits. It repeatedly enters blind alleys where it has previously been punished by faradic shock. Many experimental pigs seem less disturbed by faradic stimuli than do the controls and as a consequence they require more trials and make more errors in solving a maze problem than do the controls.

In the light of these behavioral, or, one might even say, personality, changes, it is interesting to note that the pathologic process in the brain encountered compares well with the changes described in the brains of some psychopathic persons after hypoglycemic or electrical shock treatment for personality aberrations.

NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY, AND NEW YORK NEUROLOGICAL SOCIETY

Charles Davison, M.D., *Chairman, Section of Neurology and Psychiatry, Presiding Joint Meeting, April 13, 1943*

SYMPOSIUM ON PSYCHOSOMATIC DISORDERS

Psychosomatic Medicine: A Historical Perspective. Dr. Gregory Zilboorg.

Problems of psychosomatic medicine have always been considered more or less controversial, with the partisan of extreme psychologic orientation in closer kinship with the philosophic, and especially the metaphysical, premises, from which psychiatry originated, and

the partisan of extreme organic orientation more at home in the purely physiologic speculations, from which medicine originated. This problem was first faced frankly as long ago as the early eighteenth century by Stahl, who was followed at the end of the century by Langermann and in the early nineteenth century by Ideler. By 1840 the issues were sharply drawn, with the weight pulling in favor of the more aggressive and self-assured somatologists—Friedreich ("Every mentally ill person is also physically ill") and Griesinger ("Mental disease is brain disease")—as against their equally earnest opponents—Feuchtersleben (the first to speak of the "psychobiologic totality of man"), Nasse (who stated that any physical disease produces a disturbance in the relationship of the psyche and the soma) and Jacobi (who wrote of "somatopsychic medicine," probably the first formulation [1838] of a concept and of the intent of psychosomatic medicine).

The present times are not dissimilar. The overpopularization of certain psychologic discoveries made at the turn of the nineteenth century has created a reaction against psychology and psychiatry, and medicine has tended to become extremely somatologic. The reappearance of the term and concept "psychosomatic medicine" marks a renewed attempt to produce a synthesis of the total reactions of the human personality. Whether psychosomatic medicine in this its revival is to be considered a new specialty or a new form of medicine is a question that only the future can decide. It would seem that only the true psychologic enlightenment of general medicine will produce a true scientific synthesis.

Physiologic Principles Underlying Psychosomatic Disorders. Dr. Donal Sheehan (by invitation).

Every reaction of an organism, or of its parts, to a new stimulus is superimposed on a base line which is already fluctuating and which is a reflection of the organism's response to an ever changing environment. Furthermore, the varying physiologic state of the tissue at the time of experiment may in itself determine the nature of the response. In the field of the autonomic nervous system the concept of rigid constants and invariable response is an erroneous one, which finds no support in physiology. To a lesser degree the same is true of the activity of skeletal muscle, for at each synapse in any somatic reflex pathway a primary volley, even though subliminal, conditions the state of the synapse for a second volley arriving within a short interval. The response to any stimulus therefore depends to a certain extent on the physiologic state of the synapse at the moment of arrival of the impulse, a state which must be continually fluctuating.

There is no sharp separation between the reactions in the somatic and those in the autonomic sphere. Visceral and vascular reactions are part of the organism's total adjustment to its environment, and probably every activity of skeletal muscle, even a slight shift in tonus, is accompanied by changes in the autonomic field. The reverse is equally true. The autonomic nervous system is therefore in no way independent of the somatic. The two are interdependent, a concept which is the antithesis of that expounded by Bichat at the beginning of the last century.

The physiologic requirements of any tissue must be balanced against those of all other tissues, and, with minor fluctuations, a steady "internal constitution" must be maintained. The constancy of the *milieu intérieur,* as Claude Bernard called it, is a condition not of static, but of dynamic, balance. It is maintained at a price. Forces pulling in opposite directions are equilibrated so as to give an appearance of rest. The condition has been called homeostasis by Cannon, to whose extensive studies the present understanding of its delicate balancing mechanism is owed. Rapid adjustments of this kind are the functions of the autonomic nervous system. Slower adaptations are, of course, possible through chemical and hormonal influences, so that the autonomic system cannot be considered as indispensable.

Sympathetic activity has been regarded as an emergency mechanism. To restrict the role of the sympathetic nervous system, however, to such a narrow concept would be erroneous. Autonomic adjustments are called into play at all times, and even the simple act of standing upright is a mild emergency. Certain tissues, however, are under greater sympathetic control than others, and the immediate results of removal of sympathetic innervation differ widely in various parts of the body.

The interdependence of autonomic and somatic reactions is made even more apparent by a consideration of the central nervous system, for here somatic and autonomic functions are regulated at common levels—at the medulla, at the hypothalamus and at the cerebral cortex.

An autonomic response which has been invoked in the interest of homeostatic balance or as an expression of emotional behavior may become excessive, giving rise to symptoms which have as sound a scientific basis as any produced by organic disease. The term "functional," which is applied appropriately to such illnesses, has acquired an unfortunate connotation in ordinary medical practice. There is all too often some implication that the symptoms are

"imaginary." Yet the reality of the illness is not questioned in such obviously functional disorders as carotid sinus syncope, Raynaud's syndrome or Hirschsprung's disease. In my opinion, the only essential difference is that in the latter conditions the functional disorder leads to some tangible physical sign—convulsions and loss of consciousness, pale extremities or a dilated colon.

It is my belief that many functional disturbances, if sustained, may lead to organic change In the late stages of Raynaud's syndrome, with repeated vasospasm in the hands in response to cold or emotional stress, ulcerations may appear in the tips of the fingers. More pronounced trophic changes, of a similar nature, occur in causalgia, as described by Weir Mitchell. Hemorrhagic erosions in the gastric mucosa, associated with hypermotility and hypersecretion, may follow prolonged periods of emotional tension. My thesis, then, is that disease, and in some instances actual pathologic changes, can result from functional disturbances which are frequently only exaggerations of the normal fluctuations occurring in physiologic mechanisms.

A Basis for Classification of Disorders from the Psychosomatic Standpoint. DR. LAWRENCE S. KUBIE.

Psychosomatic interrelations indicate the processes by which energies which are generated on the psychologic level of experience can be translated into disturbances of somatic function. The process of somatization is viewed as a series of successive stages in the dissociation of a physiologic process from its original physiologic purpose. The following steps are recognized: 1. Normal compensatory and synergistic physiologic mechanisms are brought into play in order to reenforce action against internal or external obstacles. 2. Because this usually occurs in a setting of a consciously perceived emotion, a conditioned link is established between the emotion and these same bodily mechanisms of reenforcement and overflow, even without stressful action. 3. The physiologic manifestations of reenforcement and overflow can occur alone, without either stressful action or conscious emotion. 4. The sustained influence of chronic unconscious inner tension can then overflow into one of four channels, involving (a) organs of external relation; (b) organs of internal economy; (c) instinctual organs, or (d) the body diffusely as a whole.

The clinical evaluation of any of these states of somatization depends (a) on the type of somatization and (b) on the psychopathologic setting in which it arises. This gives rise to a descriptive nomenclature which has clinical and prognostic implications and to a possible system of codification constructed on the foundations of the "Standard Nomenclature of Disease."

Criteria for Psychosomatic Diagnosis and Therapy, with Special Reference to Cardiovascular Syndromes. DR. HELEN FLANDERS DUNBAR (by invitation).

In spite of the rapidly increasing attention devoted to psychosomatic disorders, knowledge of diagnosis and therapy is still in what for general medicine has been called the "pre-Osler" stage. A classification of these disorders has been attempted, but an adequate nosology is still lacking. One difficulty seems to lie in the attempt to differenate psychosomatic disorders from those that are not psychosomatic, rather than to incorporate the psychosomatic approach into general medical practice.

As a preliminary basis for nosology in this field, criteria for psychosomatic diagnosis are presented. These criteria have been developed during a twelve year study of patients representing serial admissions to a large general hospital. All patients between the ages of 15 and 50 years who were suffering from any type of cardiovascular dysfunction, diabetes or fracture were studied by means of clinical, psychologic and physiologic technics simultaneously. About 1,600 patients were studied in this way, and follow-up records for about half of them were obtained for periods of from one to twelve years. Hence the distortion which often results from study of a single case of some particular psychosomatic disorder was avoided.

Analysis of the records after the preliminary period of study indicated a relation between the personality picture and the disease, although this had not been the object of the investigation. A review and check of personal and medical histories resulted in the delineation of distinct personality profiles for each syndrome. These profiles are outlined and discussed from the point of view of their diagnostic and prognostic value, as well as their use in determination of the therapeutic management best suited to the patient. Suggestions for psychosomatic therapy are outlined for each of the syndromes discussed.

The following conclusions are reached:

1. Since emotional factors play a prominent role in all illnesses, incorporation of a heading in medical textbooks to cover the diagnostic and therapeutic significance of these factors in relation to each illness would be useful, and the personality profile would add precision.

2. Although the specific personality profiles presented may need to be modified in the interests of precision and simplification (high-lighting pathognomonic factors), the evidence available suggests the following conclusions: (*a*) There are distinctive personaliy profiles associated with each illness; (*b*) these profiles are of considerable diagnostic value and should become a factor in selection of the therapeutic management best suited to a given patient, and (*c*) the more the personality profile of a patient differs from that typical of his illness, the more complicated is the therapeutic problem.

DISCUSSION ON PAPERS BY DRS. ZILBOORG, SHEEHAN, KUBIE AND DUNBAR

Dr. EDWARD WEISS, Philadelphia (by invitation): Those familiar with Osler's "Textbook of Medicine," which for so many years was standard in the United States, know that beginning with the 1892 edition, and in each succeeding edition, the opening chapter was devoted to typhoid but that the fourteenth edition, celebrating the fiftieth anniversary of the book, begins with psychosomatic medicine. Perhaps this is a significant departure and means that psychosomatic medicine has come into its own. Dr. Zilboorg has pointed out that psychosomatic medicine is only a new term for an old subject. It describes an approach to medicine as old as the art of healing itself. Physicians have always known that the emotional life had something to do with illness, but the structural concepts introduced by Virchow led to the separation of illness from the psyche of man and a consideration of disease only as a disorder of organs and cells. With this separation of disease into many different ailments came the development of specialists to attend to all of them. With the specialists came the introduction of instruments of precision, and the mechanization of medicine began. Medicine then contented itself with the study of the organism as a physiologic mechanism, impressed by blood chemistry, electrocardiography and other methods of investigation, but unimpressed by, and indeed often holding in contempt, the psychologic background of the patient, investigation of which was not considered so scientific as laboratory studies. This period may, in truth, be referred to as the "machine age in medicine." It is not to be denied that remarkable developments have occurred during this period of laboratory ascendancy, but it also must be admitted that the emotional side of illness has been almost entirely neglected.

I should like to discuss this topic, therefore, from the standpoint of general medicine. Psychosomatic medicine deals essentially with three types of disorders, and this can be illustrated by reference to the cardiovascular disorders, as Dr. Dunbar has done. First, there are the so-called *functional illnesses, usually called cardiac neuroses, in which the heart is undamaged* but symptoms, such as pain, shortness of breath and fatigue, are referred to the region of the heart. The patient may live out a normal span of years, although he continues to complain of "cardiac" symptoms. Then comes organic heart disease associated with anxiety, and here is an even more important disorder than so-called functional illness, because the patient with organic heart disease who is burdened with anxiety may, because of this extra burden, have a shorter period of life than he would otherwise enjoy. Third are the psychosomatic disorders or illnesses, such as essential hypertension, which are generally held to be in the realm of physical disease, but in which every one recognizes a large emotional element. This needs no proof. What does need proof is that emotional factors of unconscious origin are intimately related to the onset of hypertension and to the cause of the disorder. If one were to construct a working hypothesis of hypertension, one could adopt a pyramid, with the base representing heredity, the constitutional factor, probably related to the inherent hypertensive tendency, and the three sides representing the vegetative nervous system, the endocrine system and the psyche—interrelated systems—stimulation of any one of which causes a reaction in the others. The important point is that in determination of the cause and therapeutic approach to this psychosomatic disorder the question is not the consideration of any one of these various factors to the exclusion of the others but that of the interrelation of all three of them. Therefore, as Dr. Dunbar has often said, and it needs constant repetition, the treatment of illness is not a problem of either a functional or an organic condition; it is a question of the degree of importance of the one and of the other and of the relationship between them.

It is recognized that patients with psychosomatic disorders have been badly handled. The question is whether the general medical man is in a position to do better today. Is he prepared to do more than label the illness "functional" and dismiss the patient, or slap him on the back and tell him to forget it, thus implying that the disorder is imaginary or, worse, that the patient is a malingerer? The organic tradition in medicine has been responsible for this unfortunate state of affairs, and not until there is introduced into medical training the idea that psychopathology deserves equal consideration with tissue pathology will the matter be remedied. Then, I think, the general medical man will be capable of treating the emotional aspects of illness.

Medicine had its real beginning in the study of man at the dissecting table. Let it continue with the study of man not only as an anatomic and physiologic mechanism, but as a human being possessed of loves and hates, urges and passions, capable of disturbing his soul and his body.

DR. FRANK FREMONT-SMITH (by invitation): Dr. Weiss has pointed out that medicine has come a long way. I think this evening marks an epoch and that the four splendid presentations emphasize the distance that has been traveled. I remember one of my first "psychosomatic" patients: Not many years ago I was called to attend a nurse at the Boston City Hospital who could not stop crying. At that time I was working on the chemistry of body fluids and had been endeavoring, not too successfully, to produce tears in my technician by the use of tear gas. When I was called to see the nurse, I decided to take advantage of the situation and collect some tears. So I slipped two test tubes into the pocket of my white coat and went to see her. I sympathized with her and assured her that I would do all I could for her. Then I explained my research project and asked her whether she would be willing to help me in it. I pulled out the test tubes and said, "Will you hold one on each side of your nose?" She took one look at me and one at the test tubes, and immediately the tears stopped. I did not get my tears, and I had no idea how I had brought about my cure. It was not long thereafter that Dr. Dunbar called on me in Boston and told me she was working on a survey of the literature on emotions and bodily changes (Dunbar, Helen Flanders: Emotions and Bodily Changes: A Survey of Literature on Psychosomatic Interrelationships, 1910-1933, ed. 2, New York, Columbia University Press, 1938, pp. XV and 601). That encouraged me tremendously, for I had felt quite alone in collecting cases which illustrated the influence of emotions on physiologic and pathologic processes. I mention this because it was only ten years ago that Dr. Dunbar came to see me, and this evening a meeting is devoted solely to psychosomatic medicine. The war is bringing a flood of cases of acute psychosomatic disturbances in the armed forces and at home, which will influence the development of psychosomatic medicine enormously. I cannot predict in what direction. We physicians will find ourselves in many dilemmas—dilemmas of classification, treatment, etc. Shall we turn over all the psychosomatic patients to the psychiatrists (the estimates vary from 60 to 90 per cent of all patients), or shall we develop a specialty of psychosomatic medicine? I do not know the answer. Dr. Zilboorg has given both perspective and direction when he stated that within the framework of medicine psychosomatic medicine will reach its fulfilment. There are many steps on the way to that goal. In the years immediately ahead the pressure of events will tax to the utmost our ingenuity and good judgment in solving these problems. I shall close with a quotation from the "Six Year Review of the Josiah Macy Jr. Foundation," published in 1937:

"Investigations of these problems can best be conducted through integrated clinical, physiological and psychological studies within the various clinical branches; for until the family physician, the pediatrician and the surgeon, as well as the various specialists, understand and deal with psychosomatic problems, no real advance can be made. When they do so, the term itself will be obsolete, for the practice of medicine will have become the practice of 'psychosomatic medicine.'"

DR. E. D. FRIEDMAN: One must be deeply impressed by the splendid historical survey which Dr. Zilboorg has given. He showed that our medical ancestors, with less accurate methods of studying disease than we physicians possess at present, were in many respects just as wise as we are.

Dr. Sheehan's paper needs no special praise. Those who know Dr. Sheehan are aware of the characteristic thoroughness with which he works and the humility which he exemplifies in his scientific discussions.

Dr. Kubie's paper is stimulating. I am not yet quite clear on some of the details either in his paper or in that of Dr. Dunbar, for I have not had a chance to read them carefully. It would, therefore, be unfair for me to attempt their discussion without a more detailed analysis of their facts. I should, however, like to say a word in connection with Dr. Kubie's paper. He has brought up the question which was discussed many years ago, namely, the James-Lange theory of the emotions. Does the expression of the emotion induce the emotion or vice versa? For myself, I should say that the expression of the emotion and the emotion are a single entity, the response of the total organism to a given situation.

May I take this opportunity to express some of my own thinking on the subject? To my mind, the basis for psychosomatic medicine, as it is understood today, is provided by the teaching of the comparative anatomists, particularly Ariëns Kappers, who spoke of the progressive encephalization of function in the nervous system. With ascent in the phylogenetic scale, more and more of the visceral and somatic functions become localized in the brain—the

hypothalamus and the cortex. This fact, to my mind, furnishes the explanation for many of the so-called psychosomatic relations which have been mentioned this evening.

I should, also, like to refer to some of the work of the clinicians of a generation ago. I remember, as a young student in Vienna, the great Neusser's speaking of the diarrhea and glycosuria which he encountered in students during examination; through emotional stress there could be activation of the autonomic nervous system and disturbance in the glands of internal secretion. Oppenheim said it was his belief that persons subject to anxiety in early life were candidates for hypertension in later years, as a result of repeated vasomotor crises. Bergmann also spoke of the angiospastic origin of ulcer of the stomach, and he expressed the certainty that among the factors which led to vasospasm was neurotic tension. This theory has been confirmed by Dr. Harold Wolff in carefully controlled experiments. It has also been suggested to some extent by the recently reported incidence of ulcer in the United States Army.

It has been my own feeling that the frequency of diabetes among the Jewish people may perhaps be explained by the frequent necessity for the mobilization of their sugar resources for flight, in the sense suggested by Cannon. All know that hyperthyroidism may be the result of psychic shock; Oppenheim called hyperthyroidism a sympathetic neurosis. All these conditions illustrate the importance of the involuntary nervous system and the endocrine glands in the psychosomatic relations to which Dr. Weiss has referred. I have had the feeling for many years that so-called asthenic persons, with a tendency to low blood pressure, poor peripheral circulation, vertical heart and ptosis of the viscera, are apt to be psychasthenic as well; they seem to be unable to stand the emotional stresses of life.

Here I should like to say a word in favor of the much maligned Adler, who introduced the concept of organ inferiority and expressed the belief that after psychic stress persons with such defects will show symptoms referable to an organ which is constitutionally and primarily inferior. All know the story of John Hunter, who had angina pectoris and who said that his life was at the mercy of any scoundrel who wished to annoy him. It is generally recognized that speech is affected by embarrassment and fear; under such circumstances a person will hem and haw. This is an expression of a disturbance in psychosomatic relations. Finally, the best example of the psychosomatic relation is the effect of chemotherapy on the psychoses. One does not need to stress to this audience the importance of the U fibers, which connect lobule with lobule, and the association fibers, which connect lobe with lobe or hemisphere with hemisphere. I believe that under electric, metrazol or insulin shock therapy the association fibers are functionally disrupted; the engrams of memory, which are at the basis of the abnormal psychic manifestations, can be altered by a change in these association pathways. The brain is an organ, and mind or thought is an end product, or result, of the metabolism of the brain cell; so the engrams of abnormal thinking can be disturbed by shock therapy. Psychosurgery accomplishes the same purpose in a more drastic and more grossly destructive anatomic manner.

I feel, as Dr. Fremont-Smith has said, that this evening is important in that it has brought to the fore, and perhaps has focused a little more accurately, medical thinking which has been going on for a long time.

DR. LOUIS LEITER, Chicago (by invitation): Some one asked me at the beginning of this meeting whether I expected to hear facts or ideas presented. I think there has been a good representation of both. Without disparaging any of the other papers presented, I should like to pay my tribute to Dr. Dunbar's presentation, chiefly because she has been so instrumental, during all these years, in laying the basis for the reunion of body and soul in American medicine. I say "body and soul," rather than "body and mind," because, as has been stressed tonight, interrelations of the emotions and the bodily states are chiefly the concern here, rather than intellectual processes in the patient's mind. It seems to me that this is the first evening I have listened to a discussion of psychosomatic medicine in which no one has apologized for an interest in this phase of medicine. This is a healthy sign; it means that much of the defensive attitude which workers in this field have had to adopt in order to put over their ideas in the face of hostility is now unnecessary; therefore energy will be released for more vigorous work. The field of psychosomatic medicine is not an easy one. Any one can make trite statements about the obvious effects of emotions on bodily changes. On the other hand, the situation is no longer as simple as it used to be in the days of the family physician, who knew all the members of a family, their background, their ideas and feelings, and could, in a rough sense, correlate their symptoms with what he knew of their emotional makeup. The personality profiles presented by Dr. Dunbar illustrate the complexity of the situation; yet it is perhaps that very complexity which will bring light to this whole matter.

With respect to the field of cardiovascular diseases, it makes me shudder when I think of the simplicity of the cold pressor test of hypertension and compare it with the labor involved

in drawing up a personality profile. On the other hand, the personality profile may be simple compared with that which may have to be done later. There is no doubt that in the field of cardiovascular disorders one will have to engage in diagnostic experiments similar to the brilliant ones which Dr. H. G. Wolff has made. There are as yet no methods for examination of the heart comparable physiologically to those for the exteriorized gastric mucosa, but something of the sort will have to be developed. It is especially in the field of cardiovascular disorders that much of this work will have to be done, because of the importance of these disturbances from the standpoint of public health, especially in the older age groups. The problems of the child with rheumatic heart disease are not nearly so difficult, because of knowledge of the disease processes, the great human interest in children and the adaptations possible in growing persons. The older patients present a much more difficult problem. Not only are such persons suffering from the beginning of aging or physical infirmity, and from their knowledge of actual disease, but they have accumulated a great many problems of one kind and another and are thus faced with both physical and emotional decay. How many of the attacks of pulmonary congestion, precordial distress and other symptoms that afflict persons with heart failure follow visits of relatives or the reading of accounts in the newspapers of the death of this or that prominent person as the result of a "heart attack"? It is obvious that if physicians are to prepare themselves and the population for the ravages of age, they should have diagnostic criteria relatively soon and should be able to apply the proper psychosomatic treatment early in the course of these diseases, instead of after the incident has occurred, whether the incident is the occurrence of cardiac thrombosis or the statement to the patient that he has hypertension. For this reason, I feel that all have benefited a great deal from the discussion tonight and that it will act as a stimulus to the development of means of application of both the theoretic and the practical aspects of psychosomatic medicine. It is to be hoped that the end result will be not so many more psychosomaticists or cardiologists but the well rounded type of physician, who will not hesitate to make a psychologic or an emotional examination as readily as he now makes his ordinary physical examination.

DR. BETTINA WARBURG (by invitation): I think I was asked to discuss Dr. Dunbar's paper because of my work with a group of patients with coronary disease. It is a difficult paper to discuss because Dr. Dunbar did not have time to do more than put the charts on the screen as she talked of other things. This is regrettable, because they contain much interesting information and suggest many questions which cannot be raised here because of the lateness of the hour. Dr. Dunbar has done a splendid piece of pioneer work in this field, of which she has given only a brief outline. There is no doubt that she has blazed a new trail, over which many other workers will have to travel before it becomes first a road and then a paved highway.

The difficulty with the utilization of a routine questionnaire like that Dr. Dunbar used to obtain her profiles is that the answers are superficially correct but, on deeper investigation, are frequently found to conceal a tendency the reverse of the one which is indicated. If one asks a patient, "Do you get into fights?," and he answers, "No, I always cross the street to avoid them," one is led to believe that he is the most pacific person in the world, whereas his cardinal difficulty may be his inability to deal with his aggressive tendencies.

Dr. Dunbar suggests the use of such a questionnaire by the general medical practitioner, who must needs ask the question directly and has no means of interpreting the answer. He is therefore asked to depend on answers which may or may not be relevant to the patient's underlying disturbance. Such questionnaires, while undoubtedly useful, cannot as yet be relied on for a precise diagnosis, although there is no doubt that they present a valuable guide to the type of information which must ultimately be based on thorough and prolonged psychopathologic studies.

Dr. Dunbar has emphasized the need for early psychiatric intervention in prophylaxis, as well as in treatment. In this I fully concur, although I have some doubt in regard to the efficacy of such short therapy for persons with emotional constellations which are so thoroughly repressed that they require an organ conversion. By this I do not mean that such patients should be psychoanalyzed, but I consider that to point out the difficulties at a superficial level and to expect the patient to profit from such good advice is a somewhat optimistic approach to such deeply buried unconscious difficulties. I fully agree that such patients can be treated psychotherapeutically, but the real efficacy of such therapy will depend on a much better understanding of the psychopathology of the specific disease than one now has at one's disposal.

With respect to what Dr. Kubie calls "somatization," it is still obscure why or how patients select some special organ, such as the heart or the gastrointestinal tract, to express their emotional difficulties. I hope that Dr. Wolff will presently be able to explain some of these neurophysiologic problems. The medical men, the psychiatrists and the physiologists have much work to do along these lines.

Dr. Harold G. Wolff: If Dr. Zilboorg had had the time, I am sure he would have included Charles Darwin as an important name in the history of psychosomatic medicine. Darwin, in the "Expression of Emotions in Man and Animals" (New York, D. Appleton & Co., 1873), traced the heritage of human expression. He pointed the way it would be well to take in studies of psychosomatic disorder. He would have one look at man behavioristically, in a unified way, as one would look at one's dog or cat or other household animal. But with the new knowledge of anatomy and physiology the attempt was made to interpret behavior in simpler terms than the situation allowed. "Purpose" was put aside, and behavior was interpreted in terms of fixed neural patterns. For example, as Dr. Sheehan pointed out, for a time the somatic and the autonomic nervous system were separated with regard to their part in the behavior of the organism. The autonomic nervous system was considered the system of emotional expression, and the somatic nervous system had some other purpose, which was less clearly defined. Yet any one who has seen a sheep chased by a fierce dog has no doubt of the unified action of the somatic and the autonomic nervous system, both during the flight and ultimately, perhaps, in the sham death of the sheep, when it may succeed in saving its life by no longer exciting the dog in competitive running. And so man, in a competitive society, sometimes passes through a phase of tension of his muscles associated with tremor, followed perhaps by sham death (asthenia or immobilization) when the situation is too much for him. Thus, the somatic nervous system and the skeletal muscle are as much a part of the patterns of emotional expression as are the workings of the bowel, the stomach or the heart.

Dr. Sheehan also mentioned that for a time there was oversimplification of the conception of the two divisions of the autonomic nervous system. The sympathetic division was thought of as the system for emergency action and the parasympathetic system as that which enables the organism to build up its resources for the next emergency. Some believed for a time that these two functions were sharply divided. It is known now that this is not true—that in the act of one's hurdling the fence in escaping the mad bull both systems are in operation and that in the situation of recuperation, again, both are in operation. Yet there is a kind of division. For example, with feelings of withdrawal, sadness or alarm the stomach grows pale and becomes hypomotile and the secretion is diminished. The organ thus displays evidences, perhaps predominantly, of adrenergic or sympathetic function. In circumstances of agression the stomach becomes hyperacid, hypermotile and hypervascular. Acts of aggression in this instance are associated with cholinergic, and perhaps parasympathetic, activity; situations which call for retreat or withdrawal call for adrenergic and sympathetic activity. Thus, at least in the stomach, hostile aggression may be associated with cholinergic dominance. In short, in terrified and stalking animals both divisions of the autonomic nervous system and the somatic nervous system participate. The question as to which parts of the nervous system will dominate under stress is of secondary importance; of primary significance is the interplay or combination which will best serve the needs of the animal in meeting a given life situation.

As Dr. Kubie pointed out, we psychiatrists must pass through a phase of arranging our data. We must get our household in order.

Happy days are ahead. Beginning in the first year of the medical course, the students in many schools are hearing about what goes on in the body when people feel in certain ways. They "take this in their stride," just as medical students of the last century took the beautiful histologic pictures of the kidney resulting from thirty years of hypertension. There is no longer any difficulty in their acceptance of a concept that we older men perhaps have had to struggle for. But what is needed in order to make the story complete, so that it can be placed in the textbooks beside the evidence of damage from infection, new growths and physical injury, are the data that will allow the student to see what happens when an organ is too long overactive, or the effects on the organism of prolonged and excessive stress. The body can act only in a limited number of ways. Under stress of invasion of bacteria leukocytosis and fever may occur. But so may leukocytosis and fever be present with resentment or conflict. Under the stress of a chemical, such as alcohol, the gastric mucosa becomes hypervascular and the gastric secretion and the motility increase, but in an identical manner the stomach reacts to anger against one's wife. The mechanisms are limited, and pathologic manifestations so closely resemble each other that they are often indistinguishable. There will soon be available data for many organs such as are now to be had for the stomach. In the new textbooks of medicine these things will be written.

Book Reviews

An Atlas of the Basal Ganglia, Brain Stem and Spinal Cord, Based on Myelin-Stained Material. By Henry Alsop Riley, M.D. Price, $13.50. Pp. ix + 708, with 260 full page plates. Baltimore: Williams & Wilkins Company, 1943.

With the publication of this splendid atlas of Riley's, American neurology has really come of age. It is the sort of volume that will be of incalculable assistance to those patient workers in the laboratory who are all too often bewildered by the complexities of the structures under discussion and who in the past have had to refer to special works, where a confusion of names was really a babel of tongues.

The magnificent 8 by 10 inch (20.3 by 25.4 cm.) photographs of superbly sectioned and stained material are labeled with painstaking exactness. On each opposing page are the symbol for each structure and the name chosen by Riley from the numerous synonyms available. Frequently, when the whole section gives details that are insufficiently distinguishable, smaller portions are magnified, quadrants are selected and minute details are brought out vividly. On many plates more than a hundred individual structures are labeled, and when a single structure appears more than once, the number of times is indicated in parentheses. Indentification of the full name from the abbreviation on the plate is usually simple enough, but location of a structure of a given name by means of the symbol is not always easy, particularly in the complicated transition zone between the midbrain and the interbrain. Here, conceivably, coordinates would have been valuable, even as they are on small scale maps of the countries of the world. Riley has not been content with halfway measures. In addition to a superb sagittal series of infinite precision, he details two transverse and two horizontal series in order to compensate for the marked bending of the neural axis. Twenty-two transverse sections of the spinal cord illustrate almost every important structure in this part of the central nervous system.

The text is solidly informative, but not spectacular. Like the plates, it lists each separate structure with painstaking fidelity, discussing origin, direction and termination of tracts and function of cell masses when known and avoiding controversial features or the mention of different points of view. This section is particularly valuable, since the information concerning the structures is up to the minute. When a single structure is known by a number of names, Riley has chosen one from the Latin and gives in smaller type its synonyms, and then the location, functions and references to the literature, and indicates the plates in which it can be found. Cross references are abundant, so that it is possible for this volume to be used with equal facility in laboratories in all countries of the world. The bibliography is selected with care.

It is perhaps too much to expect that cellular constellations would receive the same treatment as the myelin sheath pictures, as was done in the justly famed atlases of the brains of the rabbit and the cat. Perhaps in another decade the author may summon up his courage to tackle that problem. The importance of retrograde degeneration of cells can hardly be overemphasized in connection with studies on the hodology of this portion of the brain; yet an atlas of the thalamus, hypothalamus and other cellular portions of the brain stem of man is not yet available for study in connection with material from the pathologic laboratory.

This volume has some of the fascination of the road map and Baedeker combined. The reader is almost irresistibly drawn from one section to another, as he traces the known pathways and picks up the byways, the crossroads, the canals and the cathedrals. It is in no sense a textbook of neuroanatomy; there are too many minutiae for even the expert to keep in mind. But it is an invaluable vade mecum to the neurologist and the neuropathologist harassed by the almost remembered names of some of the structures he is seeking to identify. He will find here the fibrae pallidopedunculares clearly distinguished from the fibrae perforantes pedunculi, on the one hand, and from the fasciculus subthalamopeduncularis, on the other. The plates prove it.

Physiology in Aviation. By Chalmers L. Gemmill, M.D., with a chapter on "Instrument Flight" by Lieut. Frederick B. Lee (MC) U.S.N.R. Price, $2. Pp. 129. Springfield, Ill.: Charles C Thomas, Publisher, 1943.

Man in the skies faces complications and adjustments not known to man on earth. This small handbook is the gist of a series of lectures given in the School of Aviation Medicine at Pensacola, Fla. The material is embodied in nineteen chapters, eighteen tables and the same

number of simple line figures. The book is a condensed statement of the physiology of the respiratory and the circulatory apparatus of man and the conditions which the body must meet and the compensations which it must make in order to function at high altitudes. The facts and data are simply and clearly stated. The book is essential for training of nonmedical personnel or as a thumbnail refresher course for physicians. It does not attempt to deal with the psychologic hazards of combat flight. Its usefulness would be enhanced by a list of references to more detailed presentations of the subjects discussed.

Contemporary Psychopathology: A Source Book. Edited by Silvan S. Tomkins, Ph.D., with an introduction by Henry A. Murray, M.D., Ph.D. Price, $5. Pp. xiv plus 600. Cambridge, Mass.: Harvard University Press, 1943.

This is a lazy man's way of writing a book. There is nothing to show that the editor has even read the various essays that are collected in this volume. The number of persons to whom he acknowledges indebtedness would indicate only a superior executive ability on the part of the collector, like that of the editor who got his newspaper written by starting a controversy about cats and then publishing the various "letters to the editor." The excuse for a book of this kind is specious. While some of the essays appeared originally in publications that are "not readily accessible to undergraduate readers," the majority of them are taken, "with permission of the publishers," from standard journals with large circulations which may be found in every medical library. There seems to be little discrimination in the selection of the forty-five essays included in this hodgepodge, except that the "contributions" shall have been made since 1939. Professor Murray compares this volume favorably with William Sentman Taylor's "Readings in Abnormal Psychology and Mental Hygiene" (New York, D. Appleton & Co., 1926), which is still in use, although published nearly twenty years ago. It seems to the reviewer, however, that it can no more be compared with that delightful volume than can bouillabaisse with smörgåsbord. The former volume shows the insight, the selective power and the critical adaptation of the author; the author keeps his material in hand. The present book merely reprints the published papers and binds them together. If the student can profit from such a procedure, there is not much use in courses being given in psychopathology.

Psychiatry in Medical Education. By Franklin G. Ebaugh and Charles A. Rymer. Price, $3.50. Pp. 619. New York: Commonwealth Fund, 1942.

This book gives a review of the situation in the years 1932 to 1940 concerning curriculums in medical schools and methods of teaching psychiatry in the United States. Both the basic training for all physicians and the special training for psychiatrists are discussed. Chapters I, II and III take up general aims and procedures in medical education, while chapters IV to IX deal particularly with psychiatric education. The data used come from the survey of the division of psychiatric education of the National Committee on Mental Hygiene. The third section of the book, chapters X and XI, discusses psychiatric training for the practice of the specialty.

Throughout the book one can see the influence of Adolf Meyer; in fact, the authors say that psychobiology is their leitmotif. Meyer's historic contribution is described as follows: "Until this time it had been customary to attach a single-word disease term to a newly admitted case and end the diagnosis there; Meyer insisted on complete case records including data on the many phases of the patient's life history. Thus Meyer freed psychiatry from its dependence upon the pathology of dead tissues, on the one hand, and from undue emphasis upon classificatory psychiatry, on the other. He emphasized that psychiatry must approach mental disease from several different viewpoints and this openmindedness toward mental disorder has characterized his whole teaching. Out of his work has developed much of our present-day teaching of psychiatry—the study of the normal, or psychobiology, the study of the basic principles underlying abnormal behavior, psychopathology, and the study and treatment of the patient who has developed important tools, such as the personality study, the direct and indirect examination procedures, and the life chart. His influence has spread directly to many medical schools through teachers and clinicians trained in his clinic and has reached indirectly into most psychiatric practice and teaching through the development of psychobiological principles in American psychiatry."

Pages 22 to 42 give the best concise description of psychobiology that the reviewer has seen. The book as a whole contains much information and advice for all members of a medical school, from first year candidates to the chairmen of the curriculum committee!

INDEX TO VOLUME 50

FALKIRK IN THE RAMAPOS

THEODORE W. NEUMANN, M.D.
PHYSICIAN IN CHARGE

Established 1889

THOMAS D. MACDONALD, M.D.
JOHN S. RICHARDS, M.D.
ASSOCIATE PHYSICIANS

"STANLEIGH"

A SANITARIUM
DEVOTED TO THE INDIVIDUAL CARE
OF MENTAL CASES

Located at

CENTRAL VALLEY
ORANGE COUNTY, NEW YORK

*The facilities of Falkirk have been
recommended by members of the medical profession
for a half century*

THE DEVEREUX AWARD

At the 1943 meeting of the American Psychiatric Association announcement was made of the establishment of an annual award of $500, to be made by the Devereux Schools of Devon, Pennsylvania, for an original paper on research in child psychiatry.

The rules and regulations as prescribed by the Research Committee of the American Psychiatric Association are as follows:

(1) The paper may be on any phase of Child Psychiatry, including laboratory studies, psychological analyses and approaches, biometrics, genetics, and clinical description and therapeutics.

(2) The paper should be 5000 words or less. In exceptional cases longer papers will be considered, but length will not be considered a merit. Clarity of presentation will be weighed as a factor in awarding the prize. The literature cited need not be exhaustive, but should emphasize the most important work in the subject and especially the modern writers should be cited and evaluated.

(3) In order to encourage research among the younger workers, the contestants should be limited to persons having less than fifteen years of experience in the field and no person having the rank of full professor or who is the head of an institution will be considered as a contestant for the prize. Except for these restrictions, the field is open to anyone who has direct and personal experience in the field of Child Psychiatry. In other words, an academic presentation will not be considered for the prize and only work which has been personally conducted along original lines will be considered.

(4) A paper by one author will have preference, other things being equal, over a paper submitted by two or more authors. Where multiple authorship exists, the prize, if awarded, will be divided equally among the number of authors.

(5) All papers must be submitted on or before March 1, 1944.

(6) They must be sealed and mailed to the American Psychiatric Association, Room 924, 9 Rockefeller Plaza, New York City.

(7) The author should submit the manuscript without his name appearing upon it. The award will be made by the Judges solely on the merit of the paper. Therefore, the author's name and address should accompany the manuscript in a sealed envelope.

(8) All papers will become the property of the Devereux Schools and may be used in any manner they see fit.

(9) All rules and regulations are subject to revision and approval by the Committee on Research of the American Psychiatric Association.

The announcement of the award will be made at the Annual Luncheon of the Devereux Foundation during the meetings of the American Psychiatric Association, which, in 1944, will be held at the Bellevue Stratford Hotel in Philadelphia, from May 15 to 18. The paper chosen by the Committee will be subsequently published.

SURGERY UNDER SIEGE!

♦ Steady hands, unwavering eyes...
he needs them now. Never mind the
bombs and shrapnel. Every case an
"emergency"... an endless strain, a withering
grind. But today's army field surgeon can take
it. Like the men at the guns he seldom relaxes,
but when he does, you can be sure he appre-
ciates a cheering smoke.

Add to his cheer. Send a carton of Camels
... a token of your personal appreciation for his
sacrifices. Remember—Camel is first choice in
the armed forces* ... for mildness, better taste.
See your dealer today.

1st in the Service

*With men in the Army, Navy, Marine
Corps, and Coast Guard, the favorite cigarette
is Camel. (Based on actual sales records.)
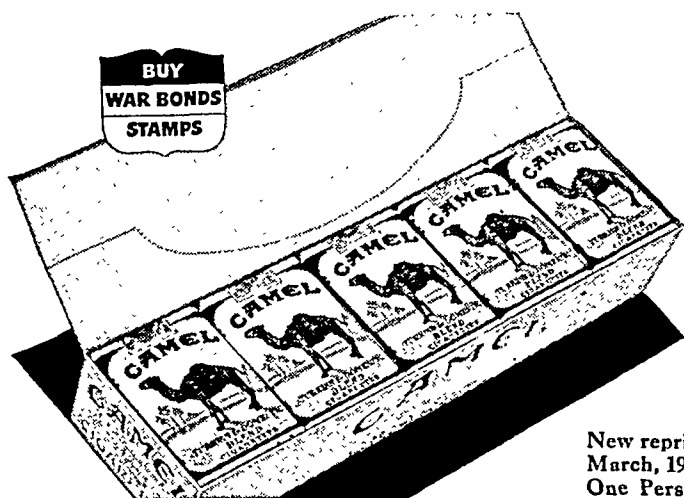
Camel
costlier tobaccos

ARCHIVES OF

NEUROLOGY AND PSYCHIATRY

EDITORIAL BOARD

VOLUME 50

1943

CONTENTS OF VOLUME 50

JULY 1943. NUMBER 1

AUGUST 1943. NUMBER 2

AUGUST—*Continued*

SEPTEMBER 1943. NUMBER 3

OCTOBER 1943. NUMBER 4

DECEMBER 1943. NUMBER 6

ARCHIVES OF

NEUROLOGY AND PSYCHIATRY

JANUARY 1944

SUBSCRIPTIONS FOR 1944 NOW DUE

Subscriptions for the current year are now due and payable—if not already paid. An envelope-remittance blank will be found in this issue. All of the periodicals published by the American Medical Association are listed on this blank, for the convenience of those who subscribe for more than one. A check mark may be placed before the name of each of the periodicals desired, or the names may be written on the lines provided. One check or draft may be sent to cover the total amount of the subscriptions.

PARALYSIS OF NERVE INDUCED BY DIRECT PRESSURE AND BY TOURNIQUET

D. DENNY-BROWN, M.B., F.R.C.P.

AND

CHARLES BRENNER, M.D.

BOSTON

Although in clinical neurology peripheral nerve palsies induced by a tourniquet are uncommon, such palsies due to direct pressure of other kinds are frequently met with. Despite this, attempts to define the factors involved in the production of such lesions have been remarkably few. Lewis, Pickering and Rothschild [1] studied the paralysis produced by the application of pressure to human limbs both by the sphygmomanometer cuff and by localized pressure on single nerves. They elicited facts of great interest. The paralysis produced by a cuff had centripetal onset and affected touch before pain and pain before motion. The latency of onset with a cuff around the upper part of the arm was almost constant (paralysis at about the twenty-fifth minute) and was the same with pressures of from 150 to 300 mm. The cuff was without effect at pressures below the systolic blood pressure. When paralysis had commenced, the placement of a second cuff below the first, with the same pressure, and then removal of the first cuff were followed by recovery from the paralysis and its reassertion after a further latency. These authors concluded therefore that such paralysis was due to ischemia of the compressed segment, and not to peripheral stasis. It was found also, however, that the nerve immediately below the cuff became less excitable than the portion farther below. They expressed the opinion that pressure influenced conduction only by means of local ischemia. The centripetal progress and selective character of the paralysis were explained by greater sensitivity of larger nerve fibers to anoxia.

Pressure confined to the ulnar nerve at the elbow, or to the peroneal nerve where it crosses the fibula, induced a paralysis and anesthesia of slower onset than those in cuff experiments, the effects appearing concurrently in all parts supplied by the nerve and sparing pain sensation. Recovery was also more rapid on release of pressure than occurred in experiments with cuffs. These differences are difficult to reconcile. Lewis, Pickering and Rothschild [1] explained them on the basis of less accumulation of metabolites in conditions of localized pressure than with the more complete occlusion of vessels by a long sphygmomanometer cuff. The late involvement of pain sense from direct pressure on human nerves had earlier

1. Lewis, T.; Pickering, G. W., and Rothschild, P.: Centripetal Paralysis Arising Out of Arrested Bloodflow to the Limb, Including Notes on a Form of Tingling, Heart 16:1-32, 1931.

1

been noted by Bastien and Vulpian[2] and by Waller.[3]   The last investigator observed that after compression of his own ulnar nerve for forty-five minutes recovery of motion and sensibility was complete only after eleven days.

These observations suggest that tourniquet paralysis is also the result of localized ischemia of the nerve at the level of the constriction, similar to that produced by a cuff.   Lesions produced by the tourniquet, however, show certain clinical points of close resemblance to lesions induced by localized pressure on nerves, such as the radial or the peroneal, and certain points of dissimilarity to the paralysis produced by the pneumatic cuff by Lewis and associates.[1]   The duration of pressure required to cause paralysis appears to be highly variable.   Thus, patients will occasionally report a radial palsy after leaning the upper part of the arm on a hard object for as short a time as twenty minutes.   Their estimate may have been faulty, but Waller, as previously noted, found persistent paralysis to result from forty-five minutes of pressure on the ulnar nerve above the elbow.   Occasionally tourniquet paralysis will be produced after an application for some forty minutes, while at other times a tourniquet is used for an hour or more without damage. Some authorities (Auchincloss[4]) have advised use of a broad cuff instead of a narrow tourniquet, claiming that the latter is more likely to cause damage to the nerve.

Further, the paralysis is, in its milder degrees, often purely motor and is not associated with reaction of degeneration; the observation of a case of this type by one of us (D. D.-B.) excited our interest in this condition.

A young man had had a surgical operation on the forefinger for an old contracture following sepsis of the flexor tendon sheath.   A tourniquet had been applied to the upper part of the arm for forty minutes.   Sensation was impaired for twenty-four hours, and complete motor paralysis below the elbow lasted ten days, after which some power of flexion of the fingers and wrist appeared.   Complete restoration of motor function occurred in about seven weeks. When he was seen four weeks after the onset, there was still no power of dorsiflexion of the wrist or fingers, and severe weakness of all the intrinsic muscles of the hand was present, though all these muscles showed normal electrical reactions and were only slightly wasted. The error of an earlier diagnosis of hysteria was apparent in the failure of the brachioradialis muscle to participate in flexion of the elbow.

This type of paralysis was evidently recognized in 1876 as due to localized pressure by Erb,[5] who said (page 393):

Even a slight mechanical action may so change the molecular constitution of the motor nerves as to abolish their power of conduction. . . . Experience teaches that motor nerves offer less resistance to such lesions than the sensory ones do.

In another place (page 424) the same author stated:

In many paralyses scarcely any alteration of electrical excitability is observed. . . . This is the rule . . . in slight traumatic paralyses as in paralysis of the radial nerve from pressure.

Later (page 551) he said:

In the slighter forms of musculospiral paralysis arising from pressure . . . the electrical excitability is usually quite normal, and it may often in such cases be satisfactorily employed

2. Bastien, J.-B., and Vulpian, A.: Mémoire sur les effets de la compression des nerfs, Gaz. méd. de Paris 10:794-795, 1855.

3. Waller, A.: On the Sensory, Motory, and Vasomotory Symptoms, Resulting from Refrigeration and Compression of the Ulnar and Other Nerves in Man, Proc. Roy. Soc.. London 12:89-102, 1862-1863.

4. Auchincloss, H.: Surgery of the Hand, in Nelson Loose Leaf Surgery, New York. Thos. Nelson & Sons, 1941, vol. 3, p. 509.

5. Erb, W. H.: Diseases of the Peripheral Cerebrospinal Nerves, in von Ziemssen. H. W.: Cyclopaedia of the Practice of Medicine, New York, William Wood & Company. 1876, vol. 11.

to determine the position of the cause of paralysis in the nerve since below the point of lesion the excitability is normal, whilst no reaction can be obtained when the current is applied above it. . . . In one case of pressure paralysis (of the musculospiral nerve) I found the previously mentioned intermediate form of reaction of degeneration.

Lüderitz [6] compressed the sciatic nerve of rabbits, with the surrounding muscle, by means of a rubber band and observed that conduction of motor impulses was abolished before conduction of sensory impulses.

Dejerine and Bernheim [7] spoke of this loss of motor conductivity with preservation of electrical excitability below the level of compression and cited a case of radial nerve palsy from pressure during sleep, with autopsy twenty-five days later. They found wallerian degeneration only in the nerve to the supinator longus muscle. Close examination of the radial nerve in the upper portion of the arm and the other branches to the forearm revealed only a granular (*grénu*) appearance of the myelin sheaths throughout these nerves, with vascular congestion at the supposed point of pressure.

Nerve injuries with dissociated effects were frequent during World War I when a bullet or a shell fragment had passed close to a nerve without actually lacerating it or tearing its sheath. Thus, of 500 cases of nerve injury, Frazier and Silbert [8] stated that as a result of compression there were complete motor paralysis in 45 per cent, complete sensory loss in 15 per cent and complete reaction of degeneration in none. The phenomenon of electrical response limited to the nerve trunk below the lesion was noted eight months after suture of the radial nerve by Platt [9] and was followed by recovery of voluntary power some months later. Perthes [10] also noted this phenomenon after war injuries and cited it as an instance of true autogenous peripheral regeneration.

A British Committee on Nerve Injuries [11] stated (page 54) that with such partial or transient damage to the nerve "the axis cylinders are damaged but Wallerian degeneration does not take place; they temporarily lose their normal conductivity but retain trophic power over the distal segment of the nerve," and, later, that "in a simple case the function of the nerve is restored within a few days or weeks." We have not found any more detailed description or illustration of this interesting lesion, although Hassin [12] made reference to the paper of von Büngner, [13] in which it is stated that just proximal to ligature of a nerve some myelinated fibers may show thinning of the myelin sheath for a segment with a full sheath both proximally and distally. Ramón y Cajal [14] described and illustrated thinning of

6. Lüderitz, C.: Versuche über die Einwirkung des Druckes auf die motorischen und sensiblen Nerven, Ztschr. f. klin. Med. **2**:97-120, 1881.

7. Dejerine, J. J., and Bernheim: Sur un cas de paralyse radiale par compression, suivi d'autopsie, Rev. neurol. **7**:785-788, 1899.

8. Frazier, C. H., and Silbert, S.: Observations in Five Hundred Cases of Injuries of the Peripheral Nerves at U. S. A. General Hospital, No. 11, Surg., Gynec. & Obst. **30**:50-65, 1920.

9. Platt, H.: The Surgery of the Peripheral Nerve Injuries of Warfare, Bristol, John Wright & Sons, Ltd., 1921.

10. Perthes, G.: Beobachtungen bei elektrischer Reizung freigelegten verletzter Nerven im vergleich mit der neurologischen und histologischen Befunde, Deutsche med. Wchnschr. **45**: 897-900, 1919; Ueber das elektrische Verhalten von Muskeln nach Durchtrennung des zugehörigen Nerven, München. med. Wchnschr. **66**:1016-1017, 1919.

11. The Diagnosis and Treatment of Peripheral Nerve Injuries, Medical Research Council, Special Report Series, no. 54, London, His Majesty's Stationery Office, 1920.

12. Hassin, G. B.: Histopathology of the Peripheral and Central Nervous System, ed. 2, New York, Paul B. Hoeber, Inc., 1940.

13. von Büngner, O.: Ueber die Degenerations- und Regenerationsvorgänge am Nerven nach Verletzungen, Beitr. z. path. Anat. u. z. allg. Path. **10**:321-393, 1891.

14. Ramón y Cajal, S.: Degeneration and Regeneration of the Nervous System, translated by R. May, London, Oxford University Press, 1928, vol. 1.

axis-cylinders where they were compressed by a mildly tight ligature, with resumption of full diameter below and with full capacity for regeneration when the nerve was sectioned distal to the ligature.

Though Lewis, Pickering and Rothschild [1] observed that the onset of paralysis following application of a pneumatic cuff is different in type from that caused by direct pressure on a nerve, our own observation on the remote result of paralysis induced by a short cuff or a tourniquet would give it close resemblance to, if not identity with, the results of prolonged localized pressure. Experimental data on the effect of localized pressure are, however, also meager.

Wier Mitchell [15] pointed out that rapid return of nerve function after its loss through compression indicated a "mechanical" interruption, as opposed to anatomic degeneration. He attempted to measure "the pressure needed to arrest the passage of nerve force" by experiments on rabbits and observed that if the sciatic nerves were compressed by a chamois leather bag containing mercury, a pressure of 20 inches (50.8 cm.) of mercury was necessary to cause loss of conduction, which failed gradually in ten to twelve seconds after the application of pressure. Restoration of conduction occurred within a similar period after release of pressure. He observed that fragmentation of the myelin sheath resulted when paralysis was thus induced. Grundfest [16] succeeded in eliminating the factor of anoxia inherent in Weir Mitchell's experiment by study of frog nerve immersed in oxygenated oil and totally enclosed within a pressure chamber. He found that a pressure of 1,000 atmospheres was necessary to abolish conduction in the nerve. At lower pressures (10,000 to 15,000 pounds [4,536 to 6,804 Kg.] per square inch [6.45 sq. cm.]), a condition of hyperexcitability resulted. In the production of clinical paralysis pressures of much less degree are effective over a period of minutes or hours. The part played by cessation of circulation then becomes the chief causative factor. Bentley and Schlapp [17] recently reported the results of acute experiments similar to our own, though electrical recording of nerve impulses was used as index of conduction and there was, therefore, no evidence of dissociation of paralysis in their observations. Further reference will be made to their work later. The following studies were directed toward determination of the relation of pressure to the onset and duration of paralysis and to establishment of the histologic nature of the "intermediate form" of partial lesion described by Erb.

METHOD

The experiments were carried out on cats anesthetized by intraperitoneal injection of pentobarbital sodium (30 mg. per kilogram of body weight). In order that the immediate effects of ischemia of a short segment of nerve might be determined, localized direct pressure was applied to a short segment of nerve in a number of preliminary acute experiments. In these experiments compression was applied directly to the exposed sciatic nerve trunk by a rubberized linen bag containing mercury under pressure (fig. 1). The brass base plate (fig. 1, at B) against which the bag compressed the nerve had rounded ends to lessen the chance of angulation of the nerve. The screw collar allowed the bag to be renewed easily and the distance from the base plate to be adjusted. The metal frame had a brass extension, not shown in the diagram, which allowed the whole instrument to be fixed rigidly in any position. The portion of the sciatic nerve in the midthigh was always used, due care being

15. Mitchell, S. W.: Injuries of Nerves and Their Consequences, Philadelphia, J. B. Lippincott Company, 1872.

16. Grundfest, H.: Effects of Hydrostatic Pressures on the Excitability, the Recovery, and the Potential Sequence of Frog Nerve, in Cold Spring Harbor Symposia on Quantitative Biology, Cold Spring Harbor, L. I., New York, The Biological Laboratory, 1936, vol. 4, pp. 179-186.

17. Bentley, F. H., and Schlapp, W.: The Effects of Pressure on Conduction in Peripheral Nerves, J. Physiol. **102**:72-82, 1943.

taken to avoid damage to the entering vessels as the nerve was freed from connective tissue and mobilized. In other experiments tourniquets of various sizes were applied to the whole thigh and the nerves studied after an interval for recovery.

In short experiments the contraction of the tibialis anticus muscle was recorded by a spring myograph on smoked paper, the nerve being stimulated by a thyratron stimulator above and below the block. As the end point of failure was considered more significant than its onset, a sensitive myograph was used, with a *stop to prevent greater excursion than* approximately 25 per cent of maximal muscle tension. Sensation was estimated simply by the reaction of the lightly anesthetized animal to a thyratron stimulus applied to a peripheral sensory branch of the nerve.

For more prolonged observation of localized pressure a clip that could be applied to the nerve under sterile operative conditions was devised. This procedure, however, raised independent problems, which will be reported separately. We found the application of a tourniquet to the external surface of the limb more satisfactory for the study of persistent histologic change, and such changes as are described here were produced by the application of rubber tubing, the ends of which were clamped together by a hemostat, so as to compress the thigh just above the knee. The surface pressure exerted by the tourniquet was estimated by the height of a mercury column just sufficient to cause mercury to flow through a thin-walled rubber tube passing under the constricting band.
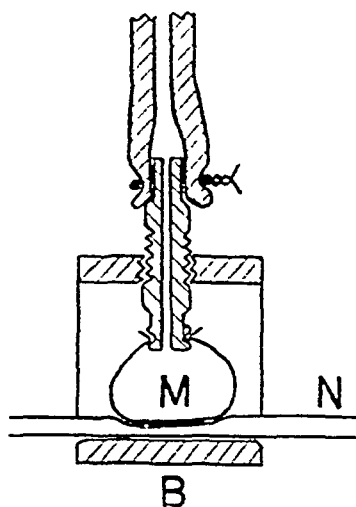
Fig. 1.—Diagram of mercury pressure bag, *M*, in relation to brass base plate, *B*, and the nerve, *N*.

IMMEDIATE RESULTS OF PRESSURE DIRECTLY APPLIED TO A NERVE TRUNK

The great variability in the effect of tourniquets and cuffs applied to the surface of the limb led us to investigate the results of pressure applied to the exposed sciatic nerve in the midthigh by means of a mercury bag. No attempt was made to follow the lesion for more than two hours after release of pressure, for the objective was to determine the relationship between pressure applied and latency of paralysis.

A repetition of Weir Mitchell's [15] mercury bag experiment disclosed that the sciatic nerve of the cat could tolerate a pressure of 20 inches (50.8 cm.) of mercury for more than two minutes without impairment of conduction or alteration of histologic structure, provided angulation of the nerve was avoided. The findings of Weir Mitchell, therefore, do not apply to the cat. A pressure of 30 inches (76.2 cm.) caused impairment of conduction to begin in twenty seconds, with almost complete failure in one hundred and twenty seconds. Recovery was complete in six minutes. At pressures of 48 inches (122 cm.) failure of conduction was complete at one hundred and sixty seconds. Sixteen minutes after release of the pressure there was complete recovery except that spreading of the toes was still feeble.

Subsequent experiments were designed to explain the effect of lower pressures, both in relation to latency of failure of conduction and to latency of recovery

when pressure was then immediately released. The relation between directly applied pressure and latency of failure of conduction is shown in graphic form (fig. 2).

It will be immediately apparent that there was considerable variation in the latency of failure of conduction at any one pressure, although in general the higher the pressure the briefer the latent period. A remarkable feature was the relative constancy in the resistance of the two sciatic nerves of the same animal. Thus, in 1 animal pressure of 30 cm. caused failure of motor conduction which was complete at twenty minutes in the right nerve and at nineteen and a half minutes
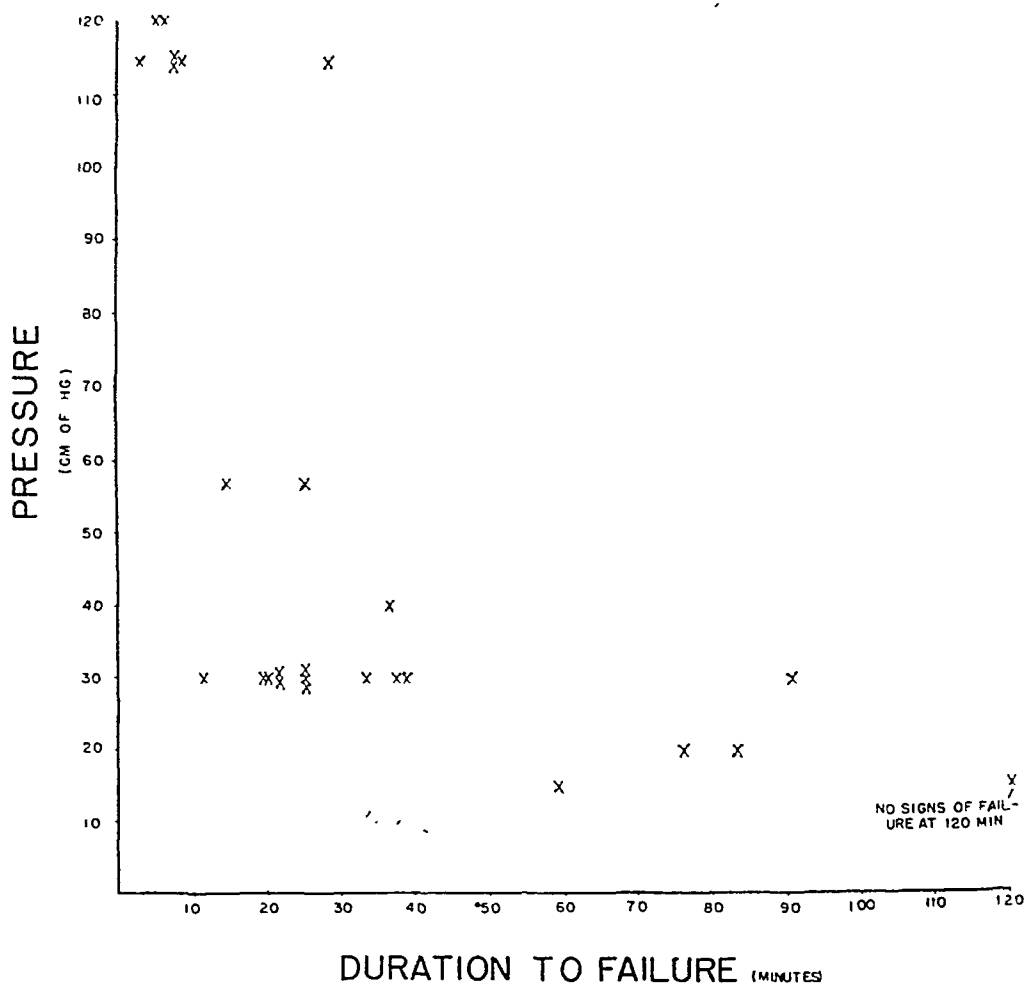
Fig. 2.—Graph showing relation of pressure to interval before onset of failure of conduction in acute experiments.

in the left nerve; in another animal the same pressure caused failure of conduction in twenty-five minutes in both the right and the left nerve. The extremes of variation in the latent period were not related to any difference in intracarotid systolic blood pressure, which regularly varied from 11 to 15 cm. of mercury. Great care was taken to obviate any kinking of the nerve by using a foot plate with rounded ends and arranging it so that it was wider than the distended bag (fig. 1). Some slight displacement of the nerve to one or the other side tends to occur as pressure is slowly increased, and it is possible that differences were related to slight variation in the extent of nerve subjected to pressure. No visible displacement was observed, however, in the major variations in the latent interval.

To examine the cause of prolonged resistance we determined the blood pressure by direct carotid manometric record and then, the bag still exerting pressure on the nerve, killed the animal and perfused the aorta with india ink in saline solution at a pressure just below the estimated systolic pressure. In cases of prolonged resistance it was found that, although the compressed segment was blanched, the perfusate had filled a large longitudinal vessel running through the compressed area in spite of the greater pressure of the contents of the bag. It is clear, therefore, that prolonged resistance to block may be due to relative protection of some vessels in the nerve. Since the sciatic nerve at the level of compression is made up of several large bundles, loosely held together by the epineurium, in which run the larger vessels, it was concluded that in such a case the escaping vessel had been protected from pressure by its lying in an interstice between the nonresistant bundles.

If this explanation is accepted for the variation in latency from case to case, it still remains to account for the shorter interval with greater pressure. A possible explanation might be that the delay in failure of conduction at the lower pressures is the result of incomplete ischemia due to diffusion of oxygen from vessels which are occluded only at the greater pressures. If this were so, there should be a minimum latent interval corresponding to the period of complete vascular occlusion. Further, the time of recovery might be expected to vary in proportion to the latent period, for the more complete the ischemia the less rapid should be the recovery. No such relationship was observed. Recovery tended either to begin immediately or to be much delayed, without relation to the pressure employed or to the latent interval of conduction failure. Thus after exposure to 56 cm. of pressure, with failure of conduction in twenty-seven minutes, recovery in 1 experiment began immediately on release. In another experiment, after failure in twenty-five minutes, recovery began six minutes after release. The duration of maintained pressure after failure of conduction should determine the rate and the degree of recovery, for, obviously, sufficiently prolonged pressure would result in necrosis. The results for short exposures were, however, again extremely variable. Thus a pressure of 30 cm. of mercury, with failure of conduction at twenty-four, nineteen and one-half, twenty-five, twenty, twenty-one and one-half and twenty-one and one-half minutes, was maintained for zero, twenty-six, twenty-five, thirty, thirty, forty and sixty minutes respectively after failure. The latent intervals of recovery were zero, thirty-six, two and thirty-seven minutes, forty-five seconds and one hundred and sixty-five and twenty minutes respectively. Thus the damage to conduction is extremely variable, probably also owing to uncontrolled escape of longitudinal vessels in the nerve, but possibly the result of a variable degree of oxygenation from the surrounding air. The compression bag and plate were kept at room temperature, which, however, did not vary greatly. In all these experiments the nerve remained fully excitable below the region of compression.

Though possibly a direct relationship could be demonstrated between duration of pressure and consequent damage if some completely fluid medium were used, the variability here found was present when the nerve was compressed against a soft bed of plasticene. As will be seen later, the variability is also present under more natural pressures.

A constant observation was a reduction in the latent period by repeated exposure to the same pressure. A pressure of 30 cm. of mercury, causing failure of conduction at sixty-five minutes, with immediate recovery on release, caused

failure at thirty-four minutes on a second exposure after a rest period of approximately ten minutes and at seven and a half minutes on a third exposure after a similar interval. In another animal 30 cm. of mercury, causing failure at thirty-seven minutes the first time, caused failure at five and a half minutes on the second compression and in five minutes on the third compression.

When failure of motor conduction was complete, sensory impulses conducted by the compressed segment of nerve were still unaffected, for peripheral electrical stimulation of a sensory branch caused a movement response in the animal as great as that from the same nerve in the opposite limb.

In none of these experiments did histologic examination of the nerve reveal any structural damage. Myelin sheaths, stained with osmic acid, and axis-cylinders, stained by the Bielschowsky method, were intact in all respects, even if a period of two hours was allowed to pass before the animal was killed and if no recovery had occurred in this time.

It is concluded, therefore, that variability in latency of failure of conduction in peripheral nerve as tested with a mercury bag is related to variability in the degree of ischemia thus brought about. The compartmented physical structure of a large nerve, like the sciatic, is such as to protect some of the longitudinal vessels from external pressure. The shorter latent period of failure of conduction with greater pressures suggests that diffusion from larger vessels results in lesser degrees of ischemia with lower pressure. The shortening of the latent period with repetition is characteristic of the behavior of peripheral nerve in anoxia (Lehmann [18]).

COMPARISON OF EFFECT OF LOCALIZED DIRECT PRESSURE AND EFFECT OF
APPLICATION OF SPHYGMOMANOMETER CUFF TO SURFACE OF LIMB

The effect of application of the mercury pressure bag to the left sciatic nerve was compared with the effect of application of an inflated cuff to the right thigh. An infant's sphygmomanometer cuff folded to give a width of 6 cm. was used. With both bag and cuff at a pressure of 15 cm. of mercury there was complete failure of conduction in the left sciatic nerve (bag) at the fifty-ninth minute. The mercury bag was released forty minutes later. Recovery of conduction began immediately and was estimated to be complete in two minutes. On the right side (cuff) there was no failure of conduction after three hours and forty-five minutes of continuous compression.

When the pressures in the bag and cuff were at 30 cm. of mercury, conduction on the left side (bag) failed completely in thirty-three minutes and that on the right side (cuff) in twenty-two and a half minutes. On both sides the pressure was continued for forty minutes after failure. On the left side recovery commenced three minutes after release, and on the right side, in two minutes. The blood pressure of the animal was 150 mm. of mercury systolic (direct reading). Carmine gelatin injected into the aorta at a pressure of 150 cm. traversed a large epineurial vessel in the compressed area of each side in spite of the presence of the bag and the cuff at a pressure of 30 cm. of mercury. These procedures were repeated with another animal, with identical results.

These observations indicate that a pressure of 15 cm. of mercury in a sphygmomanometer cuff is not equivalent to a pressure of 15 cm. of mercury on the nerve. A small tube introduced alongside the nerve showed that the effective

18. Lehmann, J. E.: The Effect of Asphyxia on Mammalian A Nerve Fibers, Am. J. Physiol. **119**:111-120, 1937.

resistance at this depth was, in fact, considerably less than that under the cuff or the tourniquet, as the following tabulation indicates.

	Resistance to External Pressure, Cm. Hg	Resistance of Internal Pressure, Cm. Hg
Sphygmomanometer cuff, 6 cm. broad..	20	12
Rubber tourniquet		
1 cm. broad..............	71	39
2 cm. broad................................	72	29
2 cm. broad................................	38	15
2 cm. broad......................	25	2.5

When, however, the external pressure exerted by the sphygmomanometer cuff was sufficiently high to cause an effective internal pressure, failure was more rapid than that with a corresponding local compression with the mercury bag. This was found to be the case even when an external cuff pressure of 30 cm. of mercury (failure in twenty-two minutes) was compared with a direct bag pressure of 40 cm. (failure in thirty-six minutes). This was probably due to the fact that the effective internal pressure produced by a 6 cm. cuff was exerted over a longer area of nerve than that compressed by the small linen bag.

The variability of the results in these experiments is not in accord with the constant failure of conduction, electrically recorded, which was observed by Bentley and Schlapp [17] twenty-five to thirty minutes after application of a 4 cm. cuff to the midthigh. These authors noted, however, that blood oozed when an artery below the compression was sectioned. They also observed failure of conduction to the ankle on stimulation either above or below a 4 cm. pneumatic cuff applied at a pressure of 24 to 28 cm. of mercury for thirty minutes. They noted that if the cuff pressure was maintained for three to four hours recovery was delayed one to two hours. In our experiments failure of conduction in the peripheral segment of the nerve did not occur in the experiments previously mentioned.

Bentley and Schlapp [19] concluded that diffusion of oxygen from surrounding tissues accounts for survival of the ischemic area of nerve. Their experiment showing shorter survival of nerve when the compressed area is wrapped in rubber membrane is, however, open to the objection that repeated anoxia lessens the latent interval to failure of conduction under identical conditions. We therefore prefer to regard the phenomenon as due to relative escape of interfascicular vessels.

PROLONGED PRESSURES AND RESULTING PARALYSIS

Attempts to apply the pneumatic cuff method of Lewis and his collaborators [1] to the hindlimb of the cat encountered difficulty, owing to the shape of the thigh of that animal. Only a narrow cuff (6 cm.) could be used. This was applied to the thigh of the anesthetized animal at a pressure of 50 cm. of mercury for two hours and six minutes. Twenty-four hours later there was paralysis of dorsiflexion of the foot and plantar flexion remained strong. There was no spreading of the toes, extension of the claws or placing. After forty-eight hours all movements had been fully recovered. In the opposite limb a pressure of 50 cm. of mercury for two hours resulted in a paralysis which had recovered completely in twenty-four hours. In another animal the same pressure, maintained for one hour, resulted in weakness (degree uncertain, owing to persistence of anesthesia) which had entirely disappeared in less than fourteen hours.

19. Bentley, F. H., and Schlapp, W.: Experiments on the Blood Supply of Nerves, J. Physiol. **102**:62-71, 1943.

These results from air pressure applied through a cuff may be compared with the following effects of tourniquets.

Summary of Data on Experiments on Paralysis Produced by Application of a Tourniquet to the Thigh *

No.	Tourni-quet †	Width, Mm.	Pressure, Cm. Hg	Duration of Pressure, Min.	Duration of Paralysis	Day on Which Animal Was Killed	Block ‡ Motor	Block ‡ Sensory	Histologic Changes §
1	R	10	30	120	Complete for 9 days	16	—	—	L
2	R	12	45	45	Nil for 18 hours	14	—	—	L (sl)
3	R	13	45	60	Nil for 18 hours	14	—	—	L (sl)
4	R	13	45	75	Weak for 5 days	7	—	—	L (sl)
5	R	12	45	75	Nil for 18 hours	14	—	—	—
6	R	12	45	90	Nil for 18 hours	7	—	—	—
7	R	12	46	90	Nil for 18 hours	14	—	—	—
8	R	12	42	90	Nil for 18 hours	7	—	—	—
9	R	11	45	120	Complete for 19 days	19	P	—	L
10	R	10	45	120	Complete for 14 days	14	P	—	L (slD)
11	R	12	49	105	Weak for 7 days	7	P	—	L (sl)
12	R	10	50	120	Complete for 7 days	7	P	—	L
13	S	2	50	120	Nil for 18 hours	7	—	—	— (sl?)
14	R	11	60	120	Complete for 14 days	16	P	—	L
15	R	10	65	120	Complete for 2 days	16	P	—	L
16	R	12	70	120	Complete for 24 hours	1	P	—	L
17	R	10	75	120	Complete for 14 days	14	P	—	L
18	R	10	75	120	Complete for 9 days	16	—	—	L
19	R	12	75	123	Weak for 12 days	14	P	—	L
20	R	12	80	120	Complete for 24 hours	1	P	—	L
21	R	12	82	120	Complete for 14 days	14	P	—	L
22	R	10	100	140	Complete for 19 days	19	P	P	L+D
23	R	10	120	60	Complete for 24 hours	2	P	—	L
24	R	10	120	120	Complete for 48 hours	2	P	—	L

* For the sake of simplicity, the observations for the peroneal nerve alone are given.
† R means a rubber tourniquet was used, and S, a string tourniquet.
‡ P indicates paralysis.
§ L indicates a lesion; L(sl), a slight lesion, and D, degeneration.

It is at once apparent that the amount and duration of pressure necessary to cause persisting paralysis are extremely variable. Since the object of these experiments was to produce a lesion, the rate of recovery after the first day was carefully studied. The speed of recovery was slow, but also variable, so that in observations 14 and 15, which were made on the same animal, conduction on the right side, at a pressure of 65 cm. of mercury, began to recover on the second day, while recovery on the left side (at a pressure of 60 cm. of mercury) began only on the fourteenth day but was more rapid, and the two sides were equally strong on the sixteenth day.

In these tourniquet experiments the animal was allowed to survive for varying intervals. Before the animal was killed the nerve was exposed and stimulated under anesthesia induced with pentobarbital sodium. Except in 1 animal, in which muscular and nervous excitability below the block was also lost, it was noted that the cat still remained sensitive to a pinch of the toe, and this retention of sensation was verified with the animal under anesthesia by stimulation of a bared sensory branch below the lesion (e. g., the musculocutaneous or the posterior tibial nerve) and comparison of the reflex movements induced from the two sides or comparison of the reflexes thus induced with those produced by stimulation of a nerve of the forelimb. A protocol will suffice to illustrate these phenomena.

EXPERIMENT (Aug. 12, 1942): Tourniquets 1 cm. wide were applied at 75 cm. of pressure to the right thigh (17 in table) and at 45 cm. of pressure to the left thigh (10 in table), each for two hours.

Complete bilateral motor paralysis without sensory impairment to pinch of the pads on the dorsum of the foot persisted until August 26, when slight plantar flexion was noted on the right side. With the animal under anesthesia induced with pentobarbital sodium, the sciatic

nerves were then exposed. Sensory conduction appeared full on each side, as judged by stimulation of the musculocutaneous nerve. On each side the sciatic nerve, split into its two divisions at the level of the great trochanter, reacted to stimulation as follows:

		Motor Response	
Nerve	Side	Above Lesion	Below Lesion
Peroneal	Right	None	Good (90%)
Peroneal	Left	None	Weak (20%)
Popliteal	Right	Moderate (50%)	Full
Popliteal	Left	Very weak (5%)	Weak (20%)

The levels at which the change in response on the right side occurred are shown in figure 3.

The data on remaining significant tourniquet experiments are summarized in the table. In 1 experiment complete loss of excitability below the level of compression was produced. and there was then associated complete loss of sensation. In 7 experiments no paralysis was seen, and in these experiments low pressure was applied for a short duration except in experiment 13, in which a narrow string tourniquet was used. In all the others, paralysis without loss of reaction to a pinch of the foot (or to stimulation of a peripheral sensory branch at the
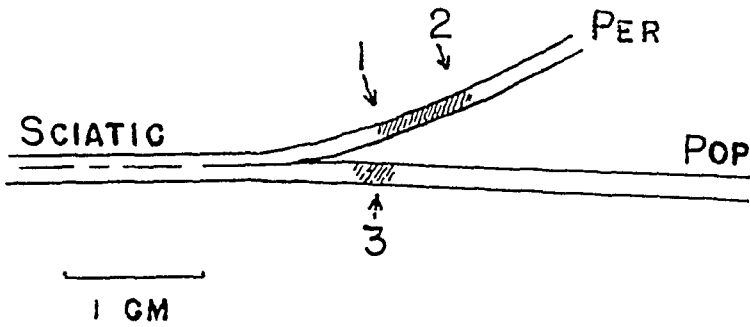
Fig. 3.—Drawing to scale showing relationship between histologic lesion (shaded) and the result of electrical stimulation in the experiment cited in the text. The arrow marked 1 indicates the most proximal point from which contraction of the post-tibial muscles could be secured. Distal to 2 the contraction was maximal. At the arrow marked 3, on the popliteal nerve. there was an abrupt change from approximately a 50 per cent strength of contraction of the post-tibial muscles when the nerve was stimulated proximally to a 100 per cent strength of contraction when it was stimulated distally.

final exposure) was produced. Recovery was usually delayed until the fourteenth to the eighteenth day and then was unusually rapid, being clinically complete in two to four days. In some instances recovery began within twenty-four hours and was complete by the fourth day. In all instances in which full recovery was noted on clinical examination of the intact animal, subsequent direct electrical stimulation of the nerve under anesthesia revealed no defect in excitability above or below the level of compression. When weakness persisted at the time of exposure of the nerve under anesthesia. the excitability was greater distal to the level of compression than proximal. The damage to conduction from above the level of compression was always greater in the peroneal nerve than in the popliteal nerve. In stimulation the proximal ends of these nerves were always split down and immediately stimulated separately. The conductivity did not rise abruptly. but increased gradually over 5 to 10 mm. of nerve (fig. 3, between arrows 1 and 2). In the animal in which all conductivity was lost (cat 22) in the peroneal nerve both above and below the level of compression, a differential still persisted in the popliteal nerve.

In an animal which had shown only slight weakness in spreading of the toes and in plantar flexion after compression with 10 mm. tourniquets for two hours at pressures of 55 and 65 cm. of mercury, respectively, repetition of compression with these tourniquets for the same period twenty-four hours after the first exposure caused no perceptible increase in the weakness.

This persisting nerve block differs considerably from a complete lesion, both in rate of recovery and in the persistence of electrical excitability in the distal segment after periods of as long as nineteen days. The muscles do not fibrillate under such circumstances, and atrophy is doubtful or absent. In 1 experiment complete degeneration of the peroneal nerve was produced on one side, and corresponding sections of the muscles confirmed the presence of atrophy only on this side, though pressure paralysis had been complete in the other nerve for nineteen days. Control experiments with crushing of the sciatic nerve in mid-thigh with a hemostat revealed that electrical excitability of the distal segment did not then return until eight weeks later. Such a lesion can also be produced when a tourniquet lesion is sufficiently severe.

HISTOLOGIC CHANGES ASSOCIATED WITH TOURNIQUET PARALYSIS

The nerves were examined routinely both by stains for myelin (osmic acid) [20] and for axis-cylinders (Gros-Bielschowsky).[21] In many cases Bodian's axis-cylinder stain, iron hematoxylin or a stain for fat (sudan III) was also used. In all cases in which the animal was killed on the same day as the experiment, even after compression for as long as two hours, or with a pressure as severe as 200 cm. of mercury, no change in myelin or in axis-cylinders was noted. The histologic changes that are characteristic of a lesion due to ischemic pressure appear within twenty-four to forty-eight hours and progress to about the tenth day. The following description applies to the lesion produced by tourniquet pressure for two hours; in every case motor excitability below the lesion was 75 to 100 per cent intact, and the gross reflex effects of stimulation of the sensory branch were unimpaired. The approximate amount of muscular contraction elicitable from above the lesion was 0 to 5 per cent.

Twenty-Four to Forty-Eight Hours.—At the end of this period, and for the next two to three days of complete motor conduction block, the only abnormality observed was slight edema of the compressed region, with a few scattered lymphocytes between the nerve fibers, and great thickening of the axis-cylinders where they were compressed (fig. 4 *A*). The increase in caliber of the axon began gradually and could be followed for 2 to 15 mm. Scattered vacuoles had appeared in the axis-cylinders, which also showed neurofibrillar condensation at the nodes of Ranvier. When such a nerve was stained with osmic acid or by some other myelin stain, the most obvious change was irregular vacuolation (fig. 4 *C*). The vacuoles appeared in the myelin of any part of the sheath. Other vacuoles were seen within the axis-cylinder, distending the sheath but not damaging the myelin. Close inspection of the nodes of Ranvier revealed a powdering of the myelin on the distal side of the cementing disk, but it was difficult to distinguish this from

20. Osmic acid method: Fix in 10 per cent concentration of solution of formaldehyde U. S. P. Cut block. Wash well in tap water for twenty-four hours and then in distilled water. Place in 1 per cent osmic acid for twenty-four hours. Wash well in tap water for twenty-four hours, embed in paraffin and section.

21. Gros-Bielschowsky method: Fix in 10 per cent concentration of solution of formaldehyde U. S. P. in saline solution; embed in pyroxylin and stain in sections, as detailed by one of us (Denny-Brown, D., in Carleton, H. M., and Lach, E. H.: Histological Technique for Normal Tissues, Morbid Changes and Identification of Parasites, ed. 2, London, Oxford University Press, 1938); counterstain with cresyl violet.

a staining artefact. The myelin sheath did not appear enlarged, and it appeared that the enlargement of the axis-cylinder was accompanied by some shrinkage of the sheath. These changes were observed over an extent of 10 to 20 mm. of nerve, the remainder appearing normal.

Seven Days.—At this interval after the application of pressure, the myelin appeared to have receded from the colorless cementing disk at the nodes of Ranvier for a distance of 0.01 to 0.04 mm. The change was most clear in the larger
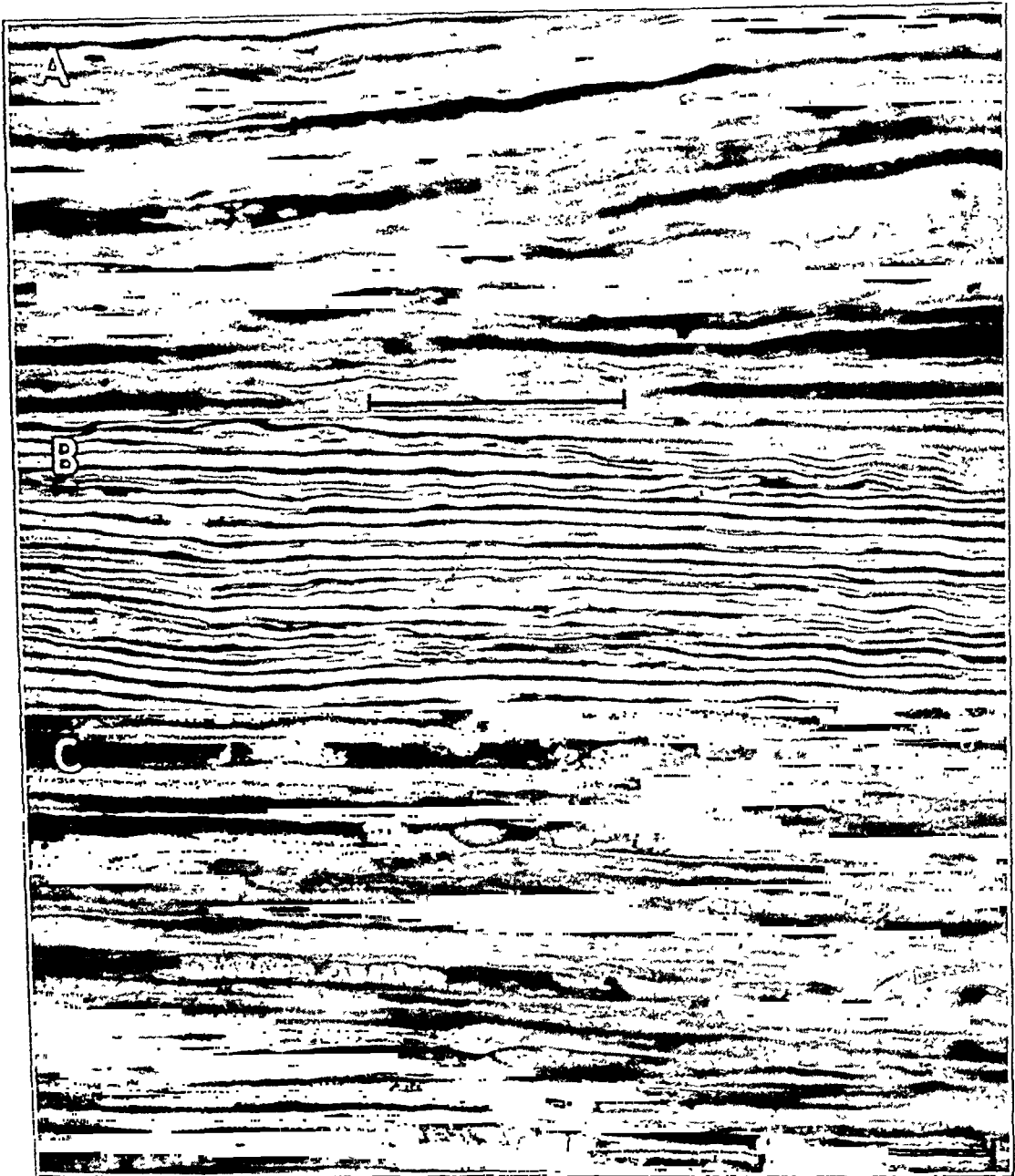
Fig. 4.—*A*, peroneal nerve; Gros-Bielschowsky method. Swelling of axis-cylinders after forty-eight hours of persistent motor paralysis following application of tourniquet at a pressure of 120 cm. of mercury for two hours. The ruled line at the bottom of this photomicrograph, and at that of *C*, is equivalent to 0.1 mm.

B, control nerve; same method and magnification.

C, peroneal nerve; osmic acid stain. Vacuolation of myelin twenty-four hours after application of tourniquet at a pressure of 80 cm. of mercury for two hours, with persisting complete paralysis.

fibers but was also noted in many of the smallest myelinated fibers. Axis-cylinder stains of the nodes of Ranvier affected in this way revealed great thinning of the

axis-cylinder through and distal to the node, corresponding to the extent of loss of myelin, with irregular unraveling of the neurofibrils. The vacuoles were no longer present. The remaining lengths of axis-cylinder were greatly swollen. The myelin distal to the node was coarsely granular, and the whole myelin sheath was ballooned out; the actual thickness of myelin, however, was reduced. The Schmidt-Lantermann incisures in the intervening region were widened and more prominent. These nodal changes were noted over a length of 10 to 20 mm., on both sides of which the nerve was of natural appearance.
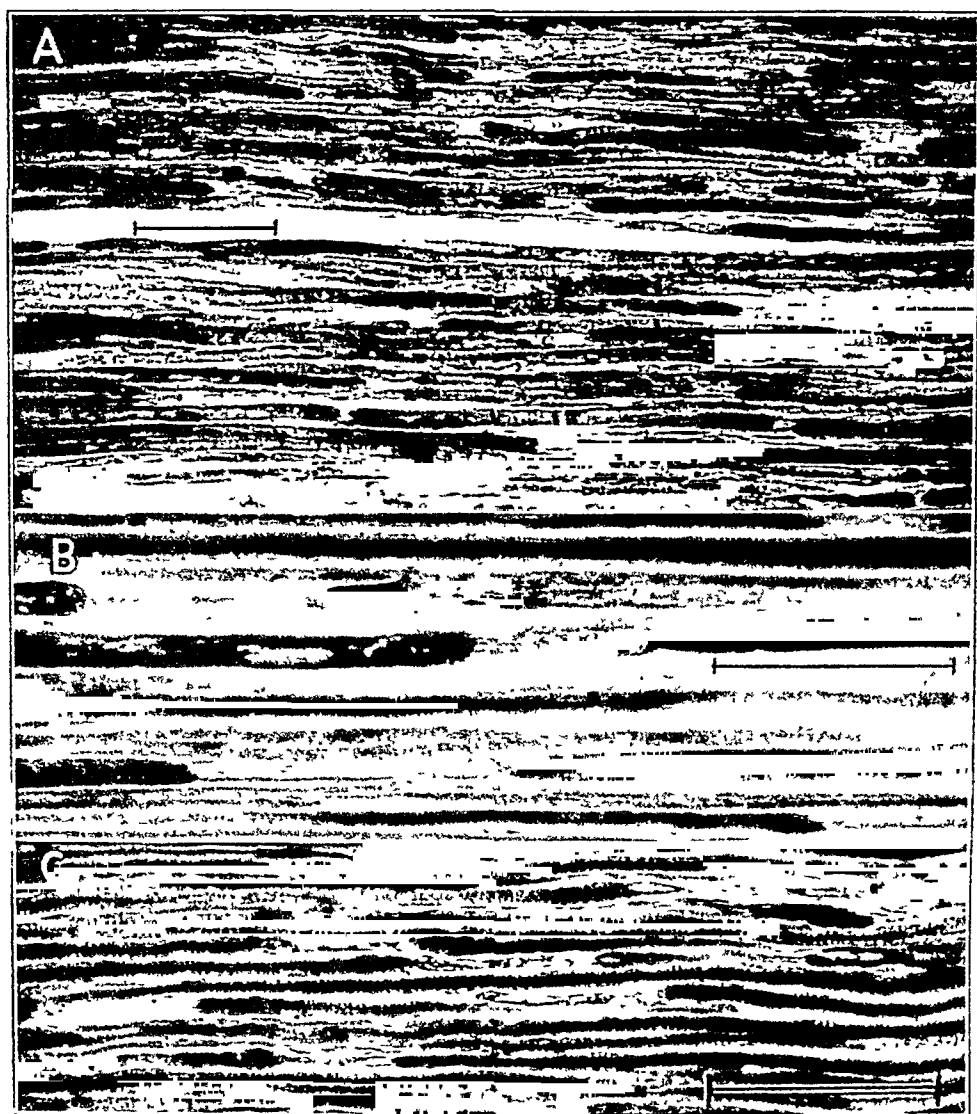
Fig. 5.—*A*, peroneal nerve; osmic acid stain. Gaps at nodes fourteen days after application of tourniquet at a pressure of 75 cm. of mercury for two hours, with persisting paralysis (same experiment as that for which diagram is shown in figure 3). The ruled line in *A*, *B* and *C* is equivalent to 0.1 mm.

B, peroneal nerve; osmic acid stain. Gaps at the nodes nineteen days after application of tourniquet at a pressure of 45 cm. of mercury for two hours (severe block).

C, popliteal nerve; osmic acid stain. Same experiment as that in which section shown in *B* was taken; minimal lesion (25 per cent block).

Two Weeks.—If this interval was allowed to elapse without improvement in the motor paralysis, the same changes were observed, and their persistence for

this period made it clear that they were not part of wallerian degeneration. The most proximal alteration was still the loss of myelin at the nodes of Ranvier, as already described, except that the gap in the myelin was in general more clearcut (figs. 5 and 6) and no granules remained. In Gros-Bielschowsky preparations many axis-cylinders failed to stain at the node of Ranvier (fig. 7) in the region of the conduction block, though the protoplasmic outline was visible (fig. 8 *A* and *B*). In others a slender, refractile, nonargentophil thread connected the thick ends of the axis-cylinders (figs. 8 *B* and *C*). More distally the gaps in the myelin sheath suddenly widened, a long strand of axis-cylinder covered by a thin myelin sheath remaining (fig. 9). The nuclei of the Schwann cells appeared not to react, for no evidence of mitosis was seen in them. There was, however, great infiltration with macrophages, some of which now regularly embraced the bared section of axon (fig. 8 *A*). The widening of the node appeared to be chiefly at the expense of the next distal myelin segment, which began suddenly with a rounded bead, often staining densely with osmic acid (fig. 9 *A* and *C*). The axis-cylinders stained feebly, or not at all, where the myelin was defective, so that at this level the contrast between the alternating thin threads and the broad remaining bands of axis-cylinders was remarkable (fig. 7 *C, D* and *E*). Irregularity and occasional vacuolation of the short, thickened segment of the axis-cylinder were evident in the region of greatest damage. Collateral appendixes of the axon appeared at intervals (fig. 8 *A* and *C*). The nerve was here edematous, with fibers widely spaced; the mesodermal elements were swollen (figs. 7 and 8), and lymphocytes were scattered through the endoneurium, sometimes in small clumps. This alteration of thinned and thickened portions of the axis-cylinder was now noted for 1 to 2 cm. The maximal diameter was approximately twice that seen in normal nerve. Farther distally the thinned segments shortened rapidly, and the thick segments lengthened and resumed normal caliber, with restoration of normal nodes of Ranvier.

For about 1 mm. distal to the last gap in a node of Ranvier, the myelin sheath was unduly swollen on either side of each node (fig. 6 *E*). Below this level no histologic defect was present. In some animals the axis-cylinders and the myelin below the lesion, while normal in other respects and conducting impulses for full contraction, showed short beaded alterations in caliber up to their junction with intact motor endings. A possible reason for this beading was the peripheral vascular stasis at the time of application of the tourniquet. Its absence in some animals and its presence above the lesion in some others, together with the lack of disturbance in function associated with it, seem to us to indicate that such beading is of little significance.

The extent of the lesion in a typical experiment and its correlation with the observed excitability below the lesion are shown in figure 3. Full conductivity was regained just above the most distal myelin gaps. The electrical stimulus may have been effective for 1 to 2 mm. beyond the point of application of the electrode, owing to spread of current.

Longer Intervals.—When the paralysis had persisted sixteen to nineteen days. the alternate thinned and thickened portions of the axis-cylinders, the edema and the mesodermal cellular reaction were still conspicuous. They were present over a length of 1.5 cm. of nerve when recovery in conduction had occurred rapidly in the previous two days. The alternate decrease and increase in caliber of the axis-cylinders and in myelin were noted, as before. The thin connecting link was more often thinly myelinated after fourteen days, or when recovery of conduction had been early, than when the animal had been killed early with still a complete block (figs. 5 *C* and 6 *B*). At the proximal extremity of the lesion

the only change in myelin was the widening of the node of Ranvier. Distal to the lesion the normal caliber and the normal nodes of Ranvier were resumed.

These changes might be present for fourteen to nineteen days without any histologic evidence of degeneration. In other cases there was greater severity of the lesion, and varying degrees of degeneration, with characteristic ellipsoids and
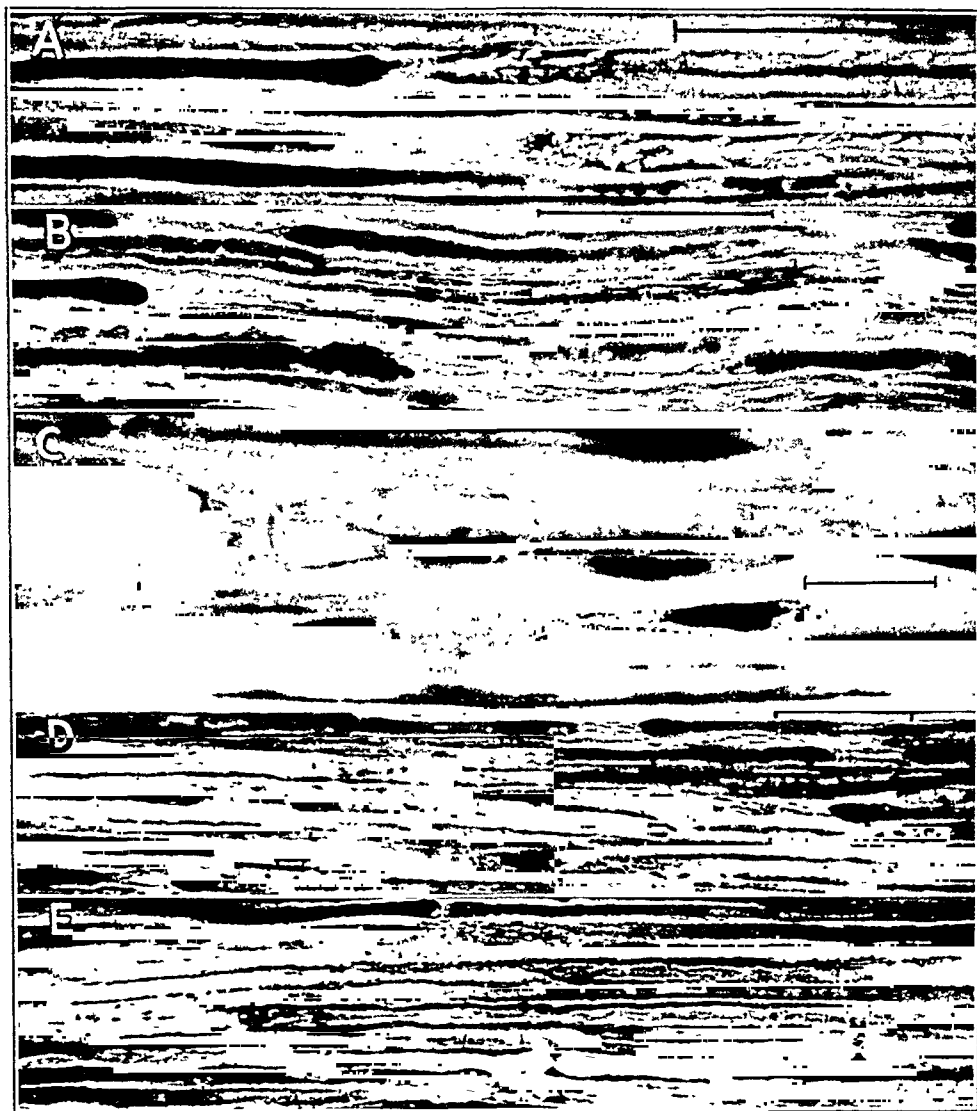
Fig. 6.—*A*, peroneal nerve; osmic acid stain. Changes in myelin fourteen days after application of tourniquet at a pressure of 45 cm. of mercury for two hours, which did not leave any persisting paralysis. The ruled line in *A* and *B* is equivalent to 0.1 mm.

B, popliteal nerve, from the same experiment as that in which section shown in figure 5 *B* was taken, illustrating the myelin covering a long gap.

C, peroneal nerve; sudan stain for fat; oil immersion lens. Changes at node after application of tourniquet at a pressure of 82 cm. of mercury for two hours, with persistent paralysis for fourteen days. The phagocyte near the sound fiber has many fat granules in the cytoplasm. The ruled line is equivalent to 0.01 mm.

D, peroneal nerve, from the same experiment as that from which the section shown in *C* was taken; osmic acid stain. Distal extremity of the lesion showing gaps in the myelin sheath. The ruled line is equivalent to 0.1 mm.

E, section 1 mm. distal to that shown in *D*, illustrating transition to normal nodes and myelin sheaths distal to the lesion. Note swellings at the nodes. Magnification same as that used in *D*.

fragmentation, accompanied the alternating increase and decrease in caliber of the remaining sound fibers. When degeneration was present below the lesion, the excitability of the nerve in this region was impaired in proportion. In a case of severe block, in which both sensation and neuromuscular excitability were lost, a
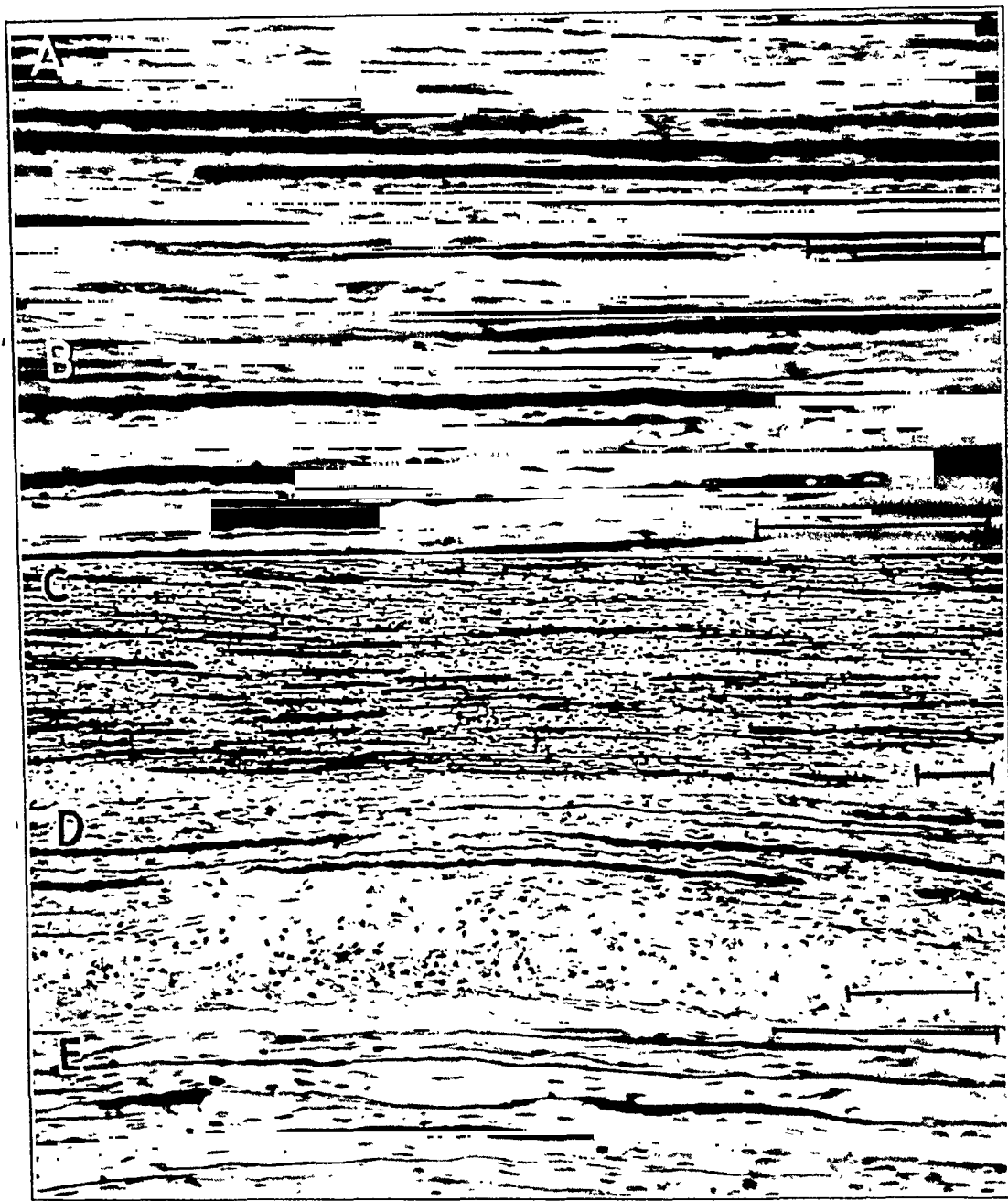
Fig. 7.—*A,* peroneal nerve, from the same experiment as that in which the sections shown in figure 6 *D* and *E* were taken; Gros-Bielschowsky method. Damage to axis-cylinders at nodes and lymphocytic infiltration, 6 mm. proximal to the area of change in myelin shown in figure 6*D* and 5 mm. distal to the area of nodal change illustrated in figure 6*C.* The ruled line in the right lower corner, and in all other portions of this figure is equivalent to 0.1 mm.

B, peroneal nerve, just proximal to the area of change in myelin illustrated in figure 5 *B;* Gros-Bielschowsky method. Change in axis-cylinders at damaged node and irregularity of staining of fine fibers.

C, popliteal nerve; Gros-Bielschowsky method: Appearance of alternate thick and thin segments of the axis-cylinder in a severe lesion nineteen days after exposure to a pressure of 100 cm. of mercury for two hours.

D, section of the same specimen of popliteal nerve as that shown in *C;* Gros-Bielschowsky and cresyl violet stains. Two myelin gaps in one fiber and cellular reaction.

E, higher magnification, showing alternate thickening and thinning illustrated in *C.*

short region in which the caliber of the fibers showed alternating increase and decrease passed into one of complete degeneration more distally.

In 3 animals pressure which had caused no observed weakness or paralysis after eighteen hours (recovery from anesthesia) had caused alternating increase
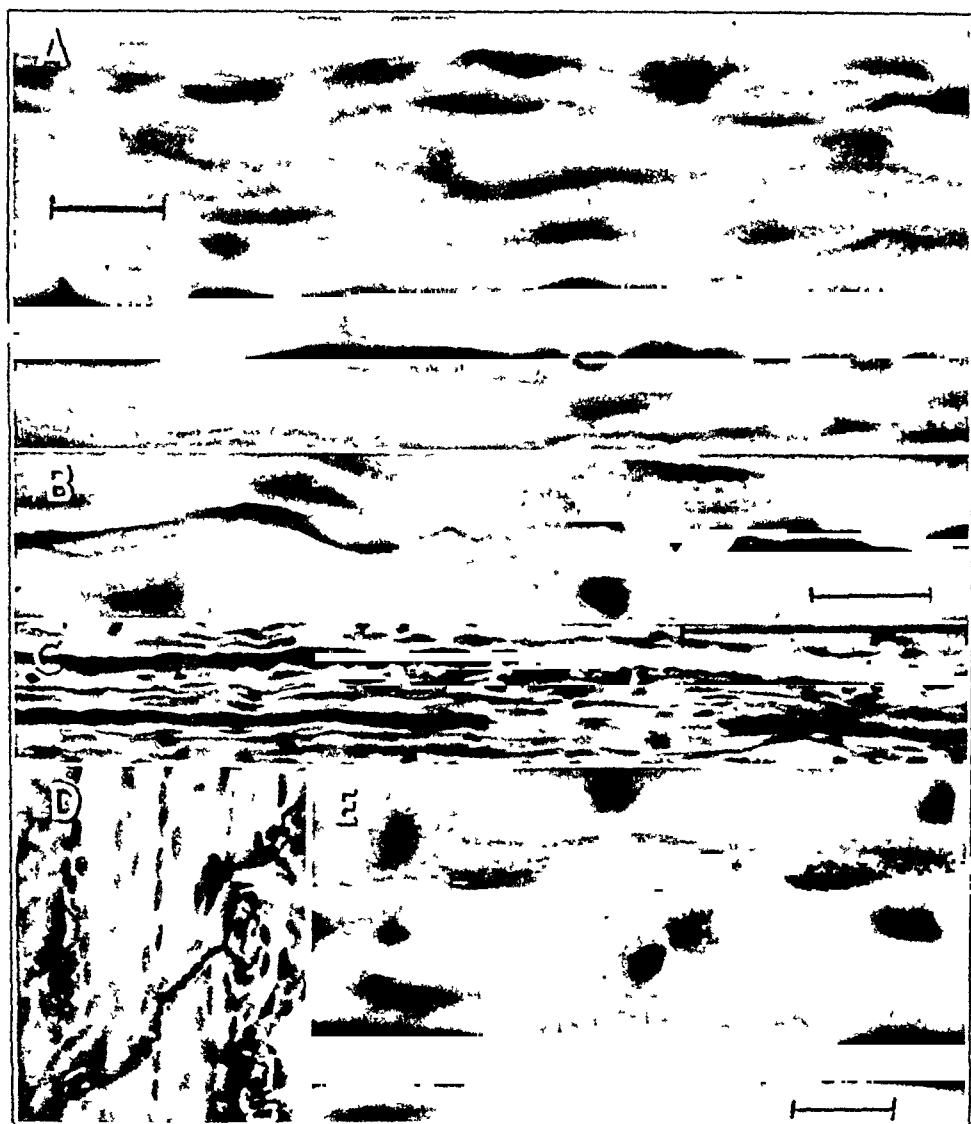
Fig 8.—*A,* popliteal nerve; Gros-Bielschowsky and cresyl violet stains. High magnification of a severe lesion persisting nineteen days after application of tourniquet at a pressure of 100 cm. of mercury for two hours, showing collaterals on a thick segment of axis-cylinder and above it two thick, but unstained, segments, with enveloping nuclei. Below is an altered nonmedullated fiber. The ruled line is equivalent to 0.01 mm.

B, section from the same nerve as that shown in *A,* indicating the appearance of an argentophil thread in a small medullated fiber connecting two irregularly thickened segments. The ruled line is equivalent to 0.01 mm.

C, higher magnification of the gap on the right side of the fiber illustrated in figure 7 *D,* showing extremely fine, wavy filament connecting two thickened axis-cylinder segments The ruled line is equivalent to 0.1 mm.

D, normal motor endings, characteristic of a large number examined in muscle paralyzed by a pressure lesion for sixteen days.

E, section from the same nerve as that illustrated in *A,* showing argentophil streaks in a thickened, but otherwise unstained, axis-cylinder, with enveloping nucleus. A phagocyte with granular cytoplasm lies between the stained and the unstained fibers The ruled line is equivalent to 0.01 mm.

and decrease in caliber of the nodes in one or two fiber bundles, the rest being unaffected. In cases in which recovery of function occurred in the first few days there was slight widening of nodes over an extent of 2 to 3 mm. of nerve, which was observed to persist as long as fourteen days, and probably longer. When conduction had commenced to recover within seven days, the changes were also usually restricted to the immediate myelin bordering the node, with gaps of 0.04 mm. or less, and such changes were observed over only 2 to 10 mm. of nerve.
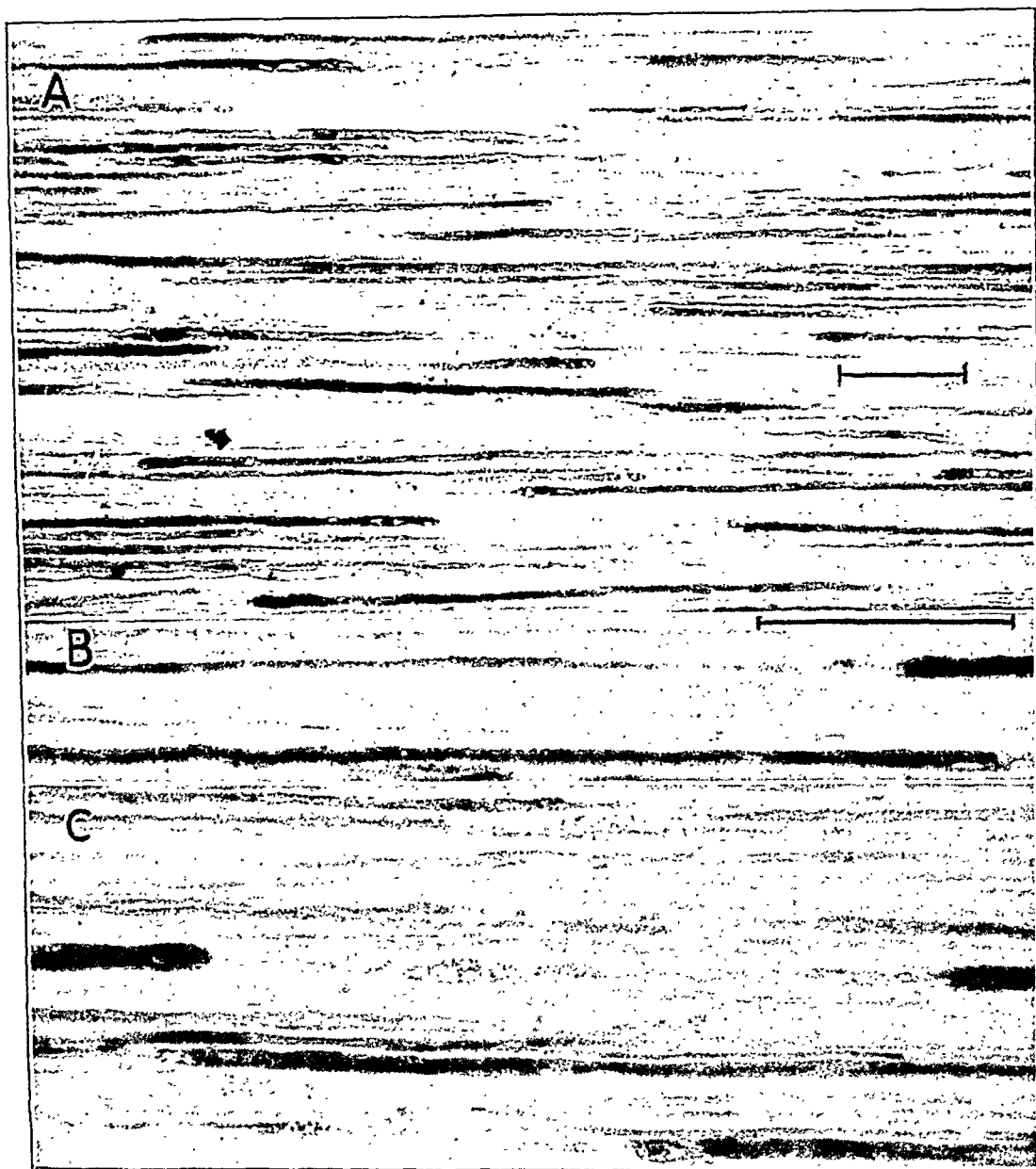
Fig. 9.—*A*, popliteal nerve; osmic acid stain. Section just proximal to the area of change shown in figure 7 *C*, illustrating the characteristic thinning and thickening of myelin segments in a severe lesion of nineteen days' duration. The ruled line is equivalent to 0.1 mm.

B and *C*, higher magnification of the section shown in *A*. The ruled line is equivalent to 0.1 mm.

Increase in severity of the lesion was therefore seen both in greater width of the myelin gap and in a longer section of nerve involved.

It is clear, therefore, that the transient forms of pressure paralysis constitute a lesion of the nerve fibers in continuity. There is loss of conduction accompanying a structural change in the nerve fiber. The most obvious change is the widening of the node of Ranvier, due to loss of myelin. This occurs in all large

fibers, and in most small fibers in any section at the level of maximal lesion. A characteristic low power view of an osmic acid preparation is shown in figure 5 *A*. Every node in the section is affected. The change in caliber of the axis-cylinder is so closely associated with damage to the myelin that it is not possible to state which is primary. Even after only twenty-four hours of paralysis, when the axis-cylinder is already swollen, the myelin at the node of Ranvier, normally thin and a little irregular, shows vacuolar change (fig. 4 *C*). Nonmedullated fibers, however, also show thinned segments and beading in the affected
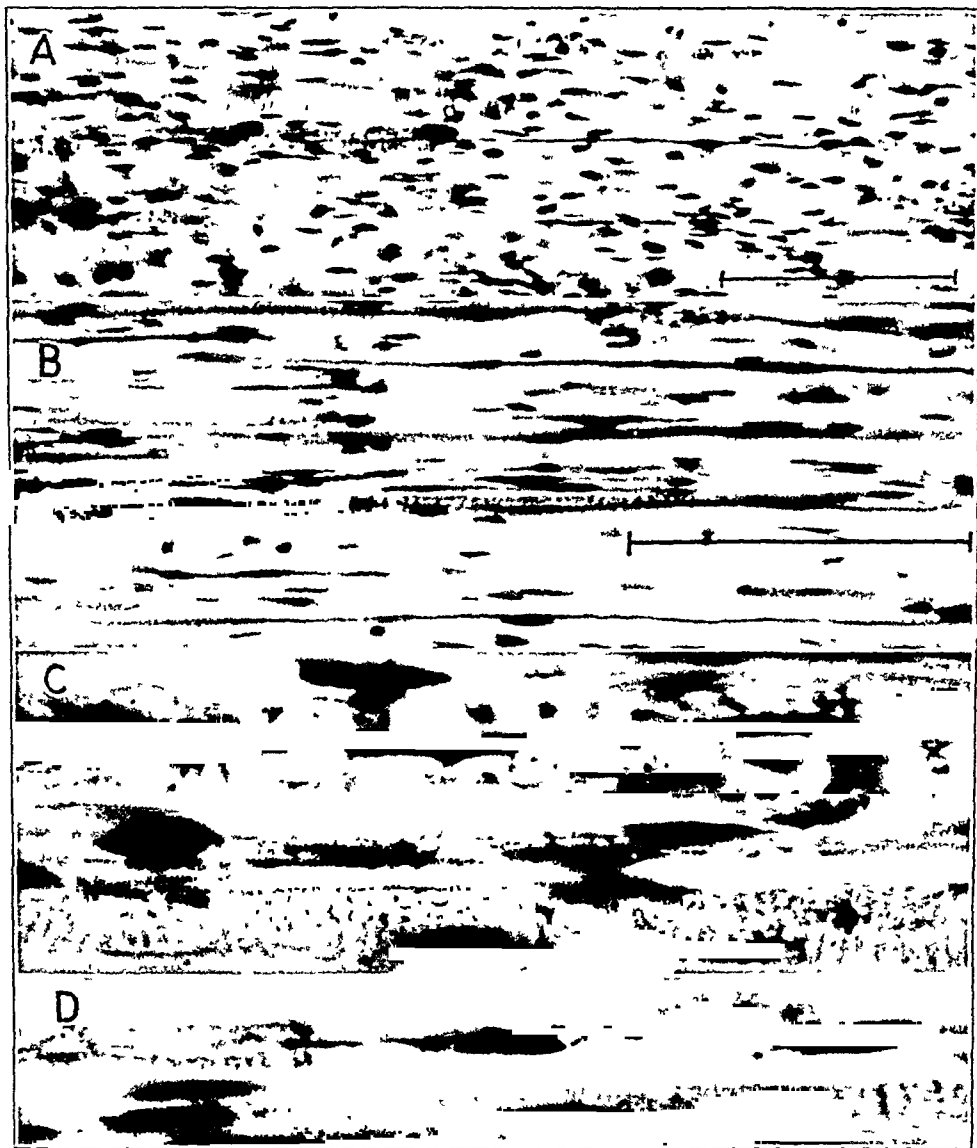
Fig 10.—*A*, popliteal nerve (iron hematoxylin stain), showing staining of a bared segment of axis-cylinder sixteeen days after application of pressure of 65 cm. of mercury for two hours. The ruled line in *A* and *B* is equivalent to 0.1 mm.

B, peroneal nerve (iron hematoxylin stain), showing staining of segments of the axis-cylinders, as compared with a sound myelinated segment in the center and a damaged node at the right upper corner.

C, from the section in *A* (oil immersion lens), showing staining of damaged axis-cylinder with iron hematoxylin above and normal myelin below.

D, from the section in *C*, illustrating the transition from bared axis-cylinder to myelinated segment.

zone (figs. 7 *B* and 8 *B*), and some vacuolation is present in finely medullated fibers in the early stages. Resumption of function appears to accompany the more general reappearance of a small, thin coating of myelin over this intervening filament, though this is seen in some gaps at all stages. At the level at which full excitability appears, and in the whole lesion for two weeks or more after recovery of conduction, the lesion differs little from that of a totally blocked nerve.

In severe lesions a cementing disk is not always visible in the myelin gap. Such interruptions are then usually opposite a Schwann nucleus (fig. 7 *D* and *E*), i. e., in the middle of the myelin segment, as well as at the node of Ranvier. Ramón y Cajal [14] (page 76) described widening of the node of Ranvier in the first two days of wallerian degeneration and the slower formation of a gap opposite the Schwann nucleus. Such changes are, then, a prelude to the fragmentation of the myelin segment. He spoke of "retraction" of the myelin, for he evidently seldom observed fatty granules. A complete pressure block of the nerve can exist for nineteen days without evidence of the usual degeneration of myelin to form ellipsoid bodies. The disappearance of myelin in the naked gaps is, however, a true dissolution, with the appearance of large vacuoles, the contents of which do not stain with osmic acid, sudan III or hematoxylin (fig. 6 *C*). The vacuoles shrink rapidly in the first seven days, leaving the Schwann sheath closely applied to the bared argentophobe axon, but are to be noted at some nodes after fourteen days. Oval mononuclear cells closely embrace the still thickened axoplasm. These have the appearance of Schwann cells, with an oval pale nucleus lying obliquely to the axon, but the absence of a nucleolus, the lack of mitosis in other Schwann cells and the abundance of wandering tissue cells lead us to identify them as histiocytes. A phagocyte filled with fat granules commonly lies near the gap in the myelin, but not closely applied to it (figs. 6 *C* and 8 *E*).

The persistence of lengths of axis-cylinder which will not take silver stains is a remarkable feature. It was observed that this region of the axis-cylinder stains deeply with iron hematoxylin, so that a section of the block stained in this way and lightly decolorized gives a picture the reverse of that of a silver stain (fig. 10). This astonishing change in the property of the surviving axis-cylinder is of considerable interest, for it indicates some relation between argentophil property and conductive function.

A further characteristic of this intermediate lesion is the slight degree or absence of disorder of sensation, so far as sensation can be judged in the experimental animal. This is true of the acute lesion (bag experiment), as well as of the chronic lesion (tourniquet experiment). In the days immediately following the establishment of an intermediate lesion there appears, in fact, to be some hyperesthesia in the form of an exaggerated withdrawal of the limb from light contact. The histologic changes in this intermediate type are certainly most obvious in large nerve fibers, but similar changes, i. e., widening of nodes and beading, are also present in small medullated fibers, and beading is noted in nonmedullated fibers. The apparent sparing of sensation would have a possible explanation on a basis of fiber size in that the tests on experimental animals fail to distinguish touch from pain were it not that in 2 clinical examples of tourniquet paralysis in man seen by one of us (D. D.-B.) there has been no disorder of touch or pain after the first few hours, whereas complete motor paralysis had persisted for two and four weeks respectively, without reaction of degeneration. In our experiments we were unable to find any size of fiber which was consistently unaffected.

The difficulty in identifying the exact length of nerve submitted to pressure by the tourniquet experiment leads to difficulty in estimating the exact degree of

spread of the lesion proximally and distally from the zone of pressure. The latter is being determined in other experiments on the production of lesions by direct pressure on the nerve, and the results will be reported later. The tourniquet experiments reveal, however, that the lesion can extend as much as 1 cm. below the original area of compression.

It would manifestly also be of interest to determine the time taken for complete restoration of histologic structure. The tourniquet method is not, however, suitable for this, owing to uncertainty of the degree of purity of the original lesion when more than three weeks is allowed for recovery, and products of degeneration are less easily recognizable. We have observed the presence of notable changes in caliber eight weeks after a localized pressure lesion.

CHANGES IN MUSCLE FIBERS

The intermediate degree of pressure lesion is found to be accompanied by paralysis of muscle, often complete, without loss of faradic excitability and without fibrillation. It is evident that the lesion blocks natural nerve impulses and those artificially stimulated at the frequency used (50 to 60 per second). We have not yet carried out experiments to determine whether conduction of impulses of slower rates or of altered impulses is possible. The muscles were observed closely during stimulation, and no evidence that even occasional full impulses reached the muscle was obtained. Section of the muscle, as compared with a corresponding section from the control leg when degeneration had occurred, revealed that atrophy was less than that on the degenerated side. The nerve endings were unaffected (fig. 8 D). The lesion, therefore, demonstrates that anatomic continuity of nerve, not receipt of impulses, prevents atrophy and fibrillation of muscle.

COMMENT

The experiments reported in this paper concern both the immediate and the remote aspects of the effect of pressure on nerve. The damaging effect of a tourniquet or a constricting cuff placed around the limb is, as Lewis, Pickering and Rothschild[1] had so clearly shown in studies of the onset of paralyses in human experiments, primarily traceable to the segments of nerve directly compressed. The effect of the vascular stasis peripheral to the cuff or tourniquet has a very slow onset at room temperature, as Lewis and his collaborators also clearly demonstrated, and does not complicate experiments of two hours' duration or less.

The work of Grundfest[10] had clearly shown that pressure in itself had no direct effect on the excitability or conductivity of nerve within the ranges of clinical possibility. Compression of mammalian nerve without angulation must be effective through the related ischemia. Our experiments have shown a great variability in susceptibility of nerves to externally applied pressures. This variability is clearly related to variable gradients of pressure in the tissues, where anatomic structure provides compartments of differing rigidity. Our experiments with direct pressure exerted on the bare nerve by a mercury bag indicated that small blood vessels can even then remain patent in the interstices between blanched nerve bundles.

These anatomic irregularities must be largely eliminated by pressure exerted over a sufficient length of nerve. The relative constancy of time which elapsed before paralysis occurred in the experiments of Lewis, Pickering and Rothschild[1] on the human arm, together with old observations on the value of a wide sphygmomanometer cuff in the measurement of blood pressure, confirms this assumption. Nevertheless, the common causative factors in pressure lesions in nerve are

applied over a short extent of nerve, and their variability in production of lesions must find explanation in variable anatomic factors.

It might be expected that ischemia would be an "all or none" effect. There is, however, a general increase in the speed of failure of conduction of nerve with increase in pressure, indicating that partial degrees of ischemia exert an identical effect over a longer period. Moreover, at all the pressures employed by us the failure of conduction was selective in that conduction of motor impulses failed before transmission of sensation.

The persistence of the nerve block for days or weeks requires not only that the ischemia persist for about two hours, but that it should be relatively complete. Thus tourniquet paralysis requires greater pressure than is needed to obstruct the main vessels to the limb. After pressure for two hours or less sensation may be impaired, but has recovered in a few hours, and the block is then usually one of motor conduction only, lasting two to eighteen days. Sufficiently intense pressure for two hours produces a more prolonged paralysis of both sensation and muscular power, lasting six to eight weeks before the first signs of recovery. The peripheral portion of the nerve is then observed to be degenerated, and the muscles are atrophic and fibrillating.

The more transient type of motor paralysis, with sparing of sensation, is evidently that described by Erb [5] in man, with what he termed an "intermediate type of reaction of degeneration," for the electrical excitability of the nerve below the lesion is retained well beyond that of a degenerating nerve. Our histologic studies have revealed that this is a disorder of conductivity of nerve without loss of anatomic continuity in the nerve fibers. This lesion is of considerable interest. The damage takes the form of intermittent attenuations of the axis-cylinder and myelin sheath. The points of least resistance are the nodes of Ranvier and the region opposite the Schwann nucleus. The early observations (twenty-four to forty-eight hours) on the lesion indicate an extensive disturbance of the protoplasm of the axis-cylinder, seen as swelling and vacuolation throughout the region subjected to compression. At this stage edema and lymphocytic infiltration have already appeared in the endoneurium. The emphasis then shifts to the myelin, which at the nodes of Ranvier becomes granular, fissured and vacuolated, with exposure of the bared or thinly covered axis-cylinder. Migrating histiocytes become filled with fat granules. The bared sector of axis-cylinder loses much or all of its affinity for silver stain and acquires an affinity for iron hematoxylin. These changes extend over a distance of 0.5 to 3 cm., beyond which normal structure is usually resumed. At the height of a severe lesion the nonmedullated segments are as long as the remainder of the myelin. Beyond this stage of severity, in which the nerve has the appearance of alternating thin and thick fibers, the thin connecting axis-cylinder presumably breaks. Once continuity is lost the distal segment degenerates, though the proximal part of the lesion has the characteristically widened nodes. The stage of the lesion short of degeneration may persist as long as nineteen days, by which time recovery of conduction is beginning to occur. Most of the thin connecting links of axis-cylinder have then acquired a fresh, thin covering of myelin. Recovery of conduction is rapid and complete, but restoration of histologic structure appears to require more than two months. We are uncertain whether it is ever complete. Throughout this period the lesion is associated with obvious mesoblastic reaction and edema, both in the endoneurium and in the epineurium. The mesoblastic reaction is itself of great interest, for lymphocytes and macrophages are mobilized and edema has occurred within twenty-four hours. The mechanism for this reaction is a matter for speculation, but it is clear that there is usually no visible damage to the blood vessels.

Under pressure the nerve is undoubtedly stretched. We have considered the possibility that the thin node of Ranvier then becomes greatly attenuated and that the thinned segment subsequently seen represents this alteration. The sheaths do not, however, reveal any such immediate change, even after extreme pressures and complete failure of conduction. The characteristic alternate thinning and thickening of the fibers develops in the course of ten days. Further, the first stage of disappearance of myelin at the node of Ranvier is identical with the first stage of degeneration of myelin distal to the lesion after nerve section, described as "retraction of myelin" by Ramón y Cajal,[14] this change then being preliminary to general fragmentation of the myelin sheath. We have presented evidence that the disorder is a dissolution of myelin, and not retraction.

The intervention of an extremely thin segment of nerve with a narrow myelin sheath between two segments of wider diameter constitutes a characteristic lesion. It closely resembles the lesion which Gombault [22] observed in 1880 in cases of lead paralysis and named "segmental periaxial neuritis." It was subsequently observed with other forms of neuritis, particularly beriberi (Pekelharing and Winkler [23]), and was produced experimentally in guinea pigs by intoxication with lead and with arsenic by Stransky.[24] The latter investigator observed that restoration of a thin myelin sheath began in the bared segment four weeks after cessation of the administration of lead. He expressed the belief that the segmental degeneration began opposite the Schwann nucleus, with increase in the corpuscles of Erzholz, and many investigators have pictured loss of myelin over one whole segment. As we have indicated, the ischemic lesion begins at the node of Ranvier, and the corpuscles of Erzholz are not increased, though secondary interruptions of the sheath occur opposite the Schwann nucleus at a later stage. The lesion is not so extensive as that in segmental periaxial neuritis. The phenomenon of ischemic lesion, as observed by us, will give added interest to the search for partial damage to nerve in other kinds of neuritis.

The lesions produced in our experiments were maximal just below the bifurcation of the sciatic nerve, at which level a tourniquet placed on the lower portion of the thigh of the cat exerts the greatest pressure. The peroneal nerve invariably showed greater defect in conduction and more severe histologic change than the popliteal nerve. The difference in the liability to damage of the two nerves in man to apparently similar injurious agents is a common clinical experience (Wilson [25]). Besides the obvious difference in size of the two nerves, the peroneal division is usually in the form of one major bundle, so that its vessels have less protection than those of the popliteal division, which lie in the crevices between the bundles. This anatomic difference may certainly account for the difference in lesions caused by pressure.

The escape of more distal segments of the nerve indicates that the peripheral stasis of circulation has little or no part in the production of the lesion, though with longer periods and at higher temperatures such an effect might be expected. We believe that the peripheral stasis in the nerve bundle is responsible for the extension of the lesion a few millimeters below the level of original compression. We are less certain of the cause of beading of the peripheral segments of the axis-cylinder and myelin. This phenomenon was inconstant and when present did

22. Gombault: Contribution à l'étude anatomique de la névrite parenchymateuse subaiguë et chronique; névrite segmentaire peri-axile, Arch. de neurol., Paris **1**:11-38, 1880.

23. Pekelharing, C. A., and Winkler, C.: Beri-Beri, Edinburgh, Young J. Pentland, 1893.

24. Stransky, E.: Ueber discontinuerliche Zerfallsprozesse an der peripheren Nervenfaser, J. f. Psychol. u. Neurol. **1**:169-199, 1902.

25. Wilson, S. A. K.: Neurology, Baltimore, Williams & Wilkins Company, 1940, vol. 1.

not interfere with conduction. Its inconstancy leads us to relate it provisionally to the stasis of the peripheral circulation and therefore to anoxia of a slightly different type from that of the localized ischemia. An attempt was made to induce ischemic lesions in nerve directly by ligation of all the vessels to the sciatic nerve in the cat (pudendal, sciatic and popliteal tributaries). No defect in conduction could be demonstrated in 3 such experiments. Injection of the aorta with india ink when the animals were killed two weeks later revealed a complete longitudinal circulation in the nerve from vessels above and below the lesion. In the nerves from these animals patchy areas of swelling of the axis-cylinders with vacuolation were observed which were identical with the earliest stage of ischemic lesions produced by the tourniquet except that these changes persisted for periods of twelve to fourteen days. Bentley and Schlapp[17] also showed the persistence of conductivity by electrical recording methods when lateral branches entering the sciatic nerve in the cat were ligated. The histologic changes observed in our experiments suggest that partial ischemia exists. It was not possible, however, to reproduce a degree of persistent partial ischemia comparable to that in a tourniquet lesion produced directly by occlusion of blood vessels.

As was previously noted, this pressure lesion affects the motor function of the nerve much more than the sensory. Though general physiologic considerations appear to relate this selective effect of ischemia to the size of the nerve fiber, the histologic features of the ischemic lesion give little support to such a hypothesis, for histologic defects are demonstrable in all sizes of fibers concurrently.

It is evident that the intermediate degree of pressure lesion with which we have been concerned is that described by Erb and cited in the introduction of this paper. In this late involvement of painful sensation, its initial instability and its pronounced delay in onset, it appears to be identical with the type of paralysis produced by localized pressure on human nerve by Lewis, Pickering and Rothschild.[1] These investigators did not proceed to the stage of lasting damage to the nerve. The studies of Lewis and Pochin[26] indicated that a tight band at the base of one finger will also induce a much later failure of sensation than will a cuff on the upper portion of the arm. The selective effect on the longest fibers in the limb (centripetal paralysis) noted by Lewis and his collaborators[1] was not investigated, but in any case this type of failure, in which defect in motor conduction was a late event, was observed by these investigators only with compression of wide extent.

The intermediate degree of ischemic lesion is also of theoretic interest in view of the evidence it offers that the structural dependence of peripheral nerve and muscle on central neuronic connection is based on anatomic continuity, and not on streams of impulses.

SUMMARY AND CONCLUSIONS

1. With compression of short segments of peripheral nerve, great variation in rate and extent of impairment of conduction is caused by uneven pressure gradients in the nerve bundles, with consequent variation in the degree of ischemia due to escape of some small vessels.

2. Under such conditions the onset of paralysis is in general more rapid the greater the applied pressure. This relationship is an expression of corresponding relative degrees of ischemia, and not a direct consequence of pressure on nerve fibers.

26. Lewis, T., and Pochin, E. E.: Effects of Asphyxia and Pressure on the Sensory Nerves of Man, Clin. Sc. **3**:141-155, 1938.

3. If care is taken to avoid angulation, no immediate structural damage is apparent within two hours after application of high pressure and resulting block of conduction.

4. The effect of pressure on conduction may be graded as of four degrees: nil; paralysis with rapid complete recovery on release of pressure; paralysis with delayed recovery without degeneration (intermediate type of pressure lesion), and complete anatomic lesion with degenerative phenomena. Attention is drawn to the third degree, which represents a lesion lasting from one to nineteen days, possibly longer, without signs of loss of excitability below the lesion and with preservation of gross sensation throughout.

5. This intermediate degree of paralysis is associated with early vacuolation and swelling of axis-cylinders and with vacuolation of myelin. After forty-eight hours there is disappearance of myelin, beginning at the nodes of Ranvier. The axis-cylinder loses its argentophil property in this region and becomes thickened in the remaining intervening segment. At a maximal stage of the lesion the demyelinated segment becomes as long as the segment retaining myelin. There is considerable mesodermal reaction. Below the region of compression the demyelinated segments progressively shorten, and normal structure is regained. In some preparations the part of the nerve distal to the site of compression shows beading of myelin and axis-cylinders. The motor end plates and muscle fibers retain their normal appearance. These histologic changes outlast the return of conductivity.

6. There is some evidence that return of conductivity is associated with the appearance of a thin coating of myelin over the previously bared segment.

7. The demyelinated argentophobe region of the axis-cylinder acquires an affinity for iron hematoxylin.

8. Loss of myelin and of the argentophil property of the axon is accompanied by loss of conductivity without loss of the trophic influence of the cell body of the neuron on the distal segment of the axon. There is no adequate explanation for the greater effect of the lesion on conduction of motor impulses.

9. From the evidence presented atrophy of paralyzed muscle appears to be prevented by anatomic connection with the motor neuron in the absence of nerve impulses.

Boston City Hospital.

ATROPHY OF BASAL GANGLIA IN PICK'S DISEASE

A CLINICOPATHOLOGIC STUDY

ANDREW J. AKELAITIS, M.D.

ROCHESTER, N. Y.

Although several observers in recent years have commented on the occurrence of changes in parts of the central nervous system other than the cerebral cortex in the condition of symmetric cortical atrophy first described by Pick, most workers continue to emphasize the cortical changes in their evaluation of the clinical signs and symptoms.

The present case is reported as a good example of the extensive changes which may occur in subcortical gray masses in Pick's disease.

REPORT OF A CASE

R. B., aged 48, a former electrical engineer, was admitted to the Rochester Municipal Hospital, March 17, 1936. He said, "The doctor says I'm nervous, but I feel swell."

Family History.—The family history was without significance.

Personal History.—The patient had been healthy prior to the present illness. He finished college at the age of 18 and up to 1932 had worked successfully as an engineer, to which profession he brought a mathematical talent. He had always been sociable and affable, but reticent, and found his interests mostly with his family.

Present Illness.—The onset was so gradual that it was difficult to state when it occurred. He lost his position in 1932 because of the economic depression and showed a normal amount of concern. He tried to patent an invention, without success, and was keenly discouraged. In 1934, two years before his admission to the hospital and five years before his death, he attempted to sell real estate but failed completely. At this time it was observed that he was unable to organize his work, that he seemed indifferent to his home and family and that he was slow in his behavior. During the six months prior to admission he seemed to age suddenly, his speech became uncertain, he stuttered and his gait took on a "mincing" quality. He showed increasing indifference to his children, became extremely meticulous in his personal habits and dress but at the table was gluttonous. In spite of enormous ingestion of food he continued to lose weight. Whereas he had always been a free spender, he became penurious. His sexual drive was increased. Deterioration in writing was evident in letters he had written to a brother. A letter written in January 1936 was normal in content and form. A letter written one month later consisted of a short but grammatically correct sentence. A letter of March 1936 showed agrammatism: Articles and conjunctions were absent, and the tense and mood of verbs were improperly employed.

Physical Status.—Physical examination revealed nothing remarkable.

Neurologic Status.—Speech was slow and dysarthric; the tongue and hands were tremulous, and the facial expression was rigid, with infrequent blinking of the eyes. Clumsiness in finer movements of the hands and occasionally a cogwheel type of rigidity in the upper extremities were evident. The gait showed a slight tendency toward propulsion.

Psychiatric Status.—He appeared confused and apathetic, and his mental processes seemed much slowed. He was correctly oriented; memory was good for remote events but much impaired for recent events, and attention and calculation were faulty. Insight was lacking, and judgment was poor. He presented a picture of moderately advanced mental deterioration of organic type.

Laboratory Studies.—The blood, urine and spinal fluid were normal.

Course in Hospital.—He remained confused, seclusive and indifferent. His only interest was the radio; he requested certain programs and supposedly read books and newspapers, the

contents of which he was unable to recall. He was discharged to his home on March 24, 1936 and was examined biannually there.

Subsequent Course of Illness.—He gradually became impulsive and childish in behavior. His scolding of the dog was like that of a 4 year old child. He performed pill-rolling movements with his thumb and forefinger, and sialorrhea became pronounced. In January 1937 he showed bilateral grasp reflexes and increased cogwheel rigidity in all extremities. He read aloud in an agrammatic manner. He could draw a house and a piston, but in writing he frequently misspelled simple words.

Mental deterioration continued, and by March 1938 he was unable to walk. He could make only peculiar clucking or sucking sounds. When an object was placed to his lips, he made sucking movements. Frequently he choked on the food given him. Neurologic
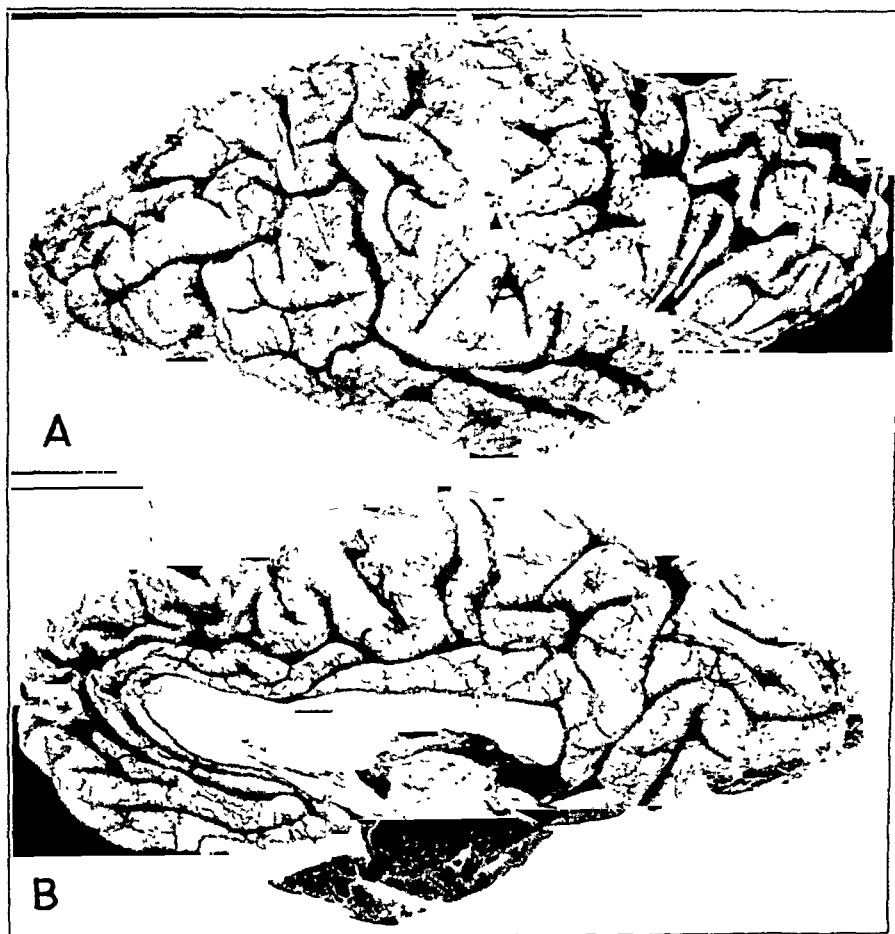
Fig. 1.—*A*, lateral view of right cerebral hemisphere, showing extreme atrophy of the frontal lobe. The process involves area 6 of Brodmann and spares the precentral gyrus and the region posterior to the rolandic fissure. *B*, mesial view of right cerebral hemisphere. The anterior portions of the frontal lobe, including the callosal-marginal (superior frontal) convolution and the anterior half of the cingular gyrus, are atrophied, while the paracentral lobule and the convolutions posterior to it are fairly well preserved. 0.8 natural size.

examination revealed spasticity with cogwheel rigidity, extreme forced innervation in both hands, occasional generalized tremors of the body and profuse salivation. The deep reflexes were hyperactive but equal on the two sides, and the plantar reflexes were normal. He was incontinent of urine and feces. Decubitus ulcers developed; the dysphagia increased, and on Jan. 23, 1939, approximately five years after onset of the disease, he died suddenly.

Gross Pathologic Observations.—Autopsy was performed four hours after death by Dr. Robert Hettig. Pulmonary emboli and bronchopneumonia were the immediate cause of death. Brown atrophy of the heart and mild arteriosclerosis were noted.

The brain weighed 910 Gm. The leptomeninges were edematous, thick and slightly adherent to the atrophied gyri. The atrophy involved the frontal lobes symmetrically, and the demarcation between the atrophied areas and the normal convolutions was sharp (fig. 1 A). Mesially, the anterior portions of the frontal lobe, including the callosal-marginal (superior frontal) convolution and the anterior half of the cingular gyrus, were atrophied, and the anterior half of the corpus callosum was notably thinned (fig. 1 B). On section, the entire ventricular system was observed to be dilated, especially the anterior horns of the lateral ventricles. The caudate nucleus (head, body and tail) was almost completely destroyed bilaterally, the structures being replaced by a deep brown area of pigmentation (fig. 2 A). The ventricular surface was deeply corrugated in this area. The thalamus, subthalamic nucleus and substantia nigra on both sides had a rusty coloration. The globus pallidus was shrunken and deeply pigmented bilaterally. The region of the nucleus of the terminal stria also had a deep brown
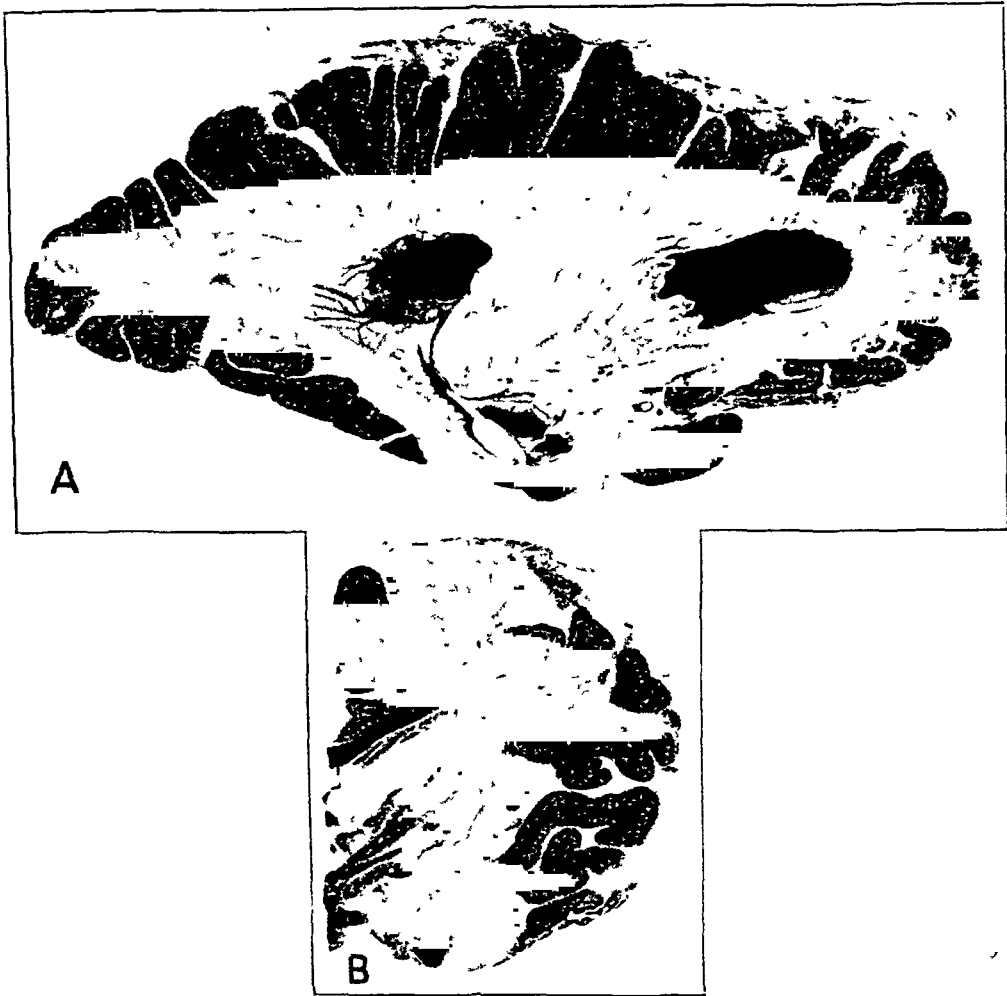
Fig. 2.—*A*, sagittal section of right cerebral hemisphere through the pulvinar, the external geniculate body, the head of the caudate nucleus and the putamen. Note the almost complete destruction of the caudate nucleus and the corrugated ventricular surface in this region. 0.8 natural size. *B*, transverse section of left cerebral hemisphere through the optic chiasm and the anterior commissure. The globus pallidus is much shrunken and has a deep rust color. The head of the caudate nucleus is almost completely destroyed. The region of the nucleus of the terminal stria is deeply pigmented. The putamen and claustrum are well preserved. Natural size.

coloration (fig. 2 B). The midbrain and hindbrain were diminished in size. The cerebellum was normal in size and appearance.

Microscopic Examination.—With von Braunmühl's stain no senile plaques were seen. Bielschowsky's silver stain revealed no argentophilic bodies. Many of the neurofibrillae of the diseased nerve cells and their processes were ballooned. This was especially apparent in the most severely involved areas, such as area F E, the subthalamic nucleus and the globus pallidus. Turnbull's stain revealed small amounts of iron pigment in the atrophied cortex of the frontal lobes. In the subcortical nuclear masses, on both sides, enormous quantities

of iron were noted in the globus pallidus and the subthalamic nucleus, and a lesser amount in the substantia nigra (especially the zona reticulata) and the nucleus of the terminal stria. Surprisingly, no iron was seen in the greatly atrophied caudate nucleus. No iron was noted in the putamen, the amygdala, the red nucleus, the cerebellum or the nuclei of the hindbrain. The iron was present in the form of minute granules in the cytoplasm of diseased and normal-appearing nerve cells and in oligodendrocytes and astrocytes and was lying free in the paren-
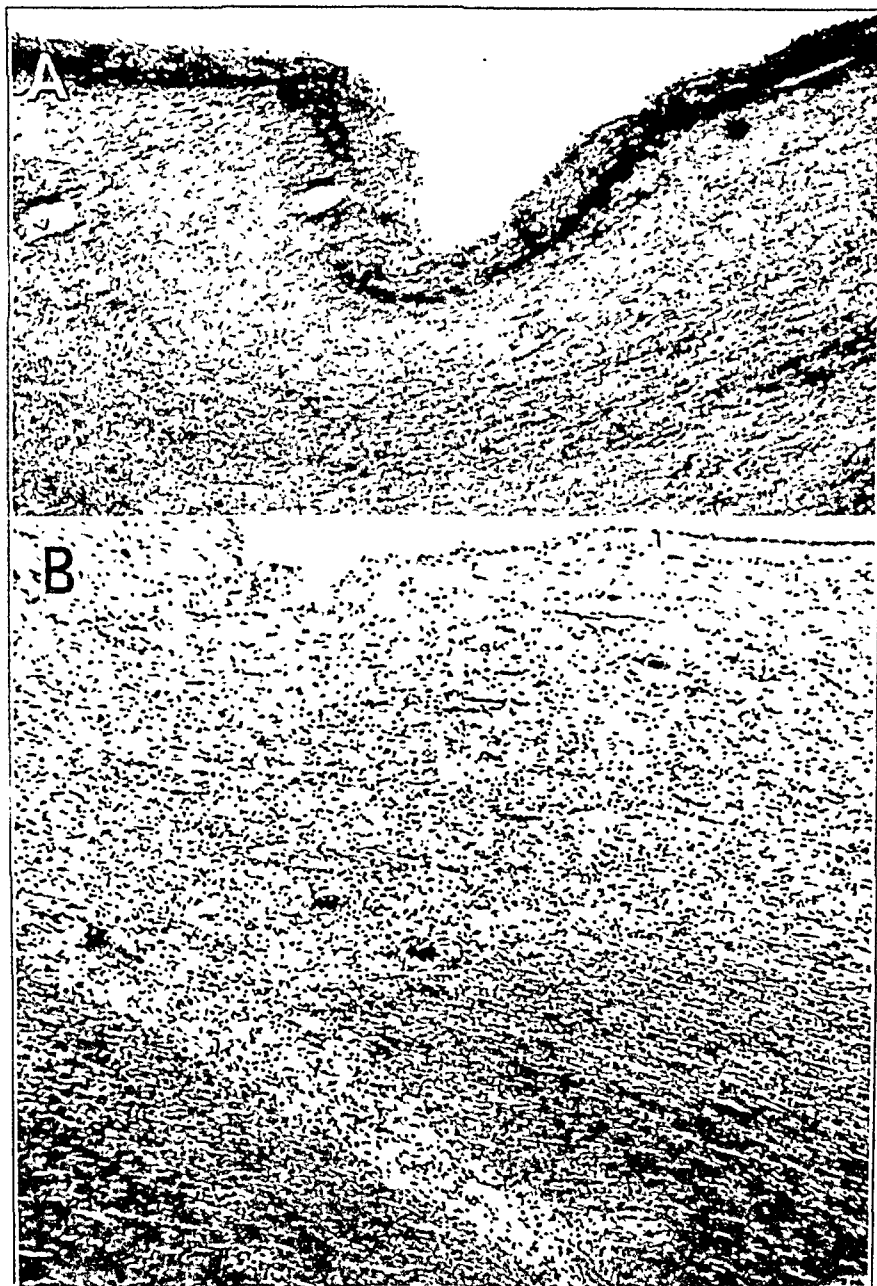
Fig. 3.—A, photomicrograph of section from left caudate nucleus, showing excessive sub-ependymal gliosis. The entire caudate nucleus is shrunken and replaced by moderate gliosis. Mallory's phosphotungstic acid hematoxylin stain. B, section from the same region as that represented in A, showing almost complete disappearance of myelin in the caudate nucleus. The internal capsule is well myelinated. The ependymal lining is not hyperplastic. There is an apparent great increase in the number of glial nuclei throughout the entire caudate nucleus. Smith-Quigley stain; × 100.

chyma. This occurred both in the cortex and in the subcortical nuclear masses already mentioned. In the latter, large clumps of iron were also noted in the neuroglia and lying

free in the parenchyma. No iron was seen in the walls of the blood vessels or in the perivascular spaces.

Stains for fat (scarlet red) showed only occasional globules of neutral fat in the perivascular spaces of the globus pallidus and the subthalamic nucleus. Little fat was seen in the atrophied cortex or the caudate nucleus. Throughout the brain, droplets of orange-staining substances, probably lipochromes, were seen in the cytoplasm of the lipophilic nerve cells. Glial stains (Holzer and the Mallory phosphotungstic acid hematoxylin) disclosed an excessive glial feltwork, with an apparently considerable increase in the number of nuclei throughout the portions of the central nervous system most severely involved (fig. 3 A).

Myelin stains (Pal-Weigert and Smith-Quigley stains) showed diffuse loss of myelin throughout the white matter of the atrophied cortex, with the U fibers relatively better pre-
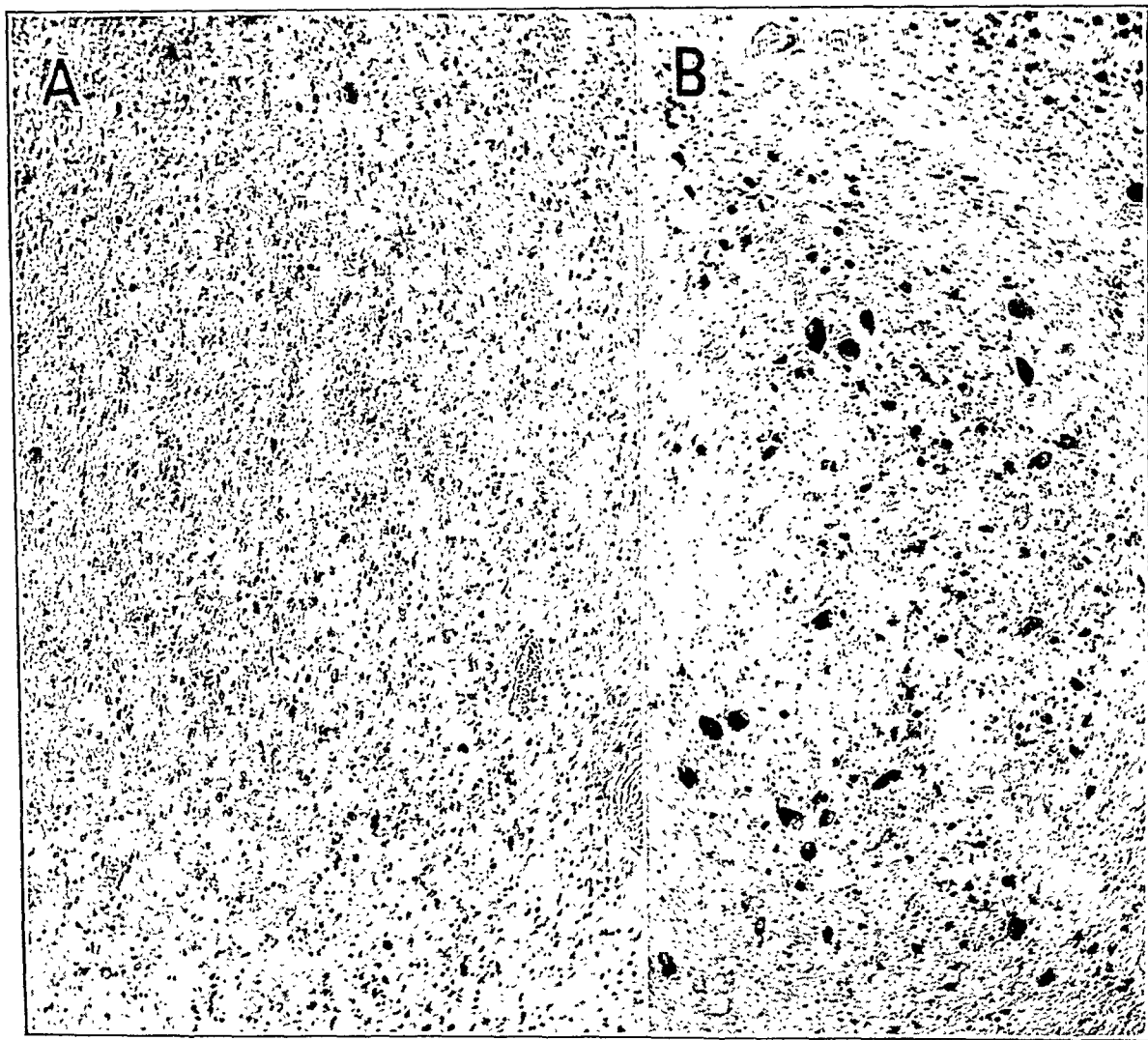
Fig. 4.—A, photomicrograph of section from left subthalamic nucleus (corpus Luysi). Only two neurons are visible, and both are swollen and filled with lipochromes. The darkly staining, round bodies observed predominantly in the lower half of the field stain intensely blue with Turnbull's stain. B, photomicrograph of section from right substantia nigra. A few normal-appearing, melanin-containing nerve cells are seen. However, the predominant picture is that of masses of melanin lying free in the parenchyma. No melanin was seen in the perivascular spaces. With Turnbull's stain very little iron was seen in this involved area, but iron was moderately abundant in the zona reticulata. Thionine stain; × 100.

served. In the caudate nucleus the myelin was practically destroyed (fig. 3 B) but was well preserved in the subadjacent internal capsule and in the putamen. In the globus.pallidus the internal and, to a less degree, the external medullary laminas were pale. · The region of the ansa lenticularis was almost completely devoid of myelinated fibers. The fasciculus lenticularis (field H 2) and the subthalamic fasciculus had fewer fibers than normal. In the cerebral peduncles there was diffuse diminution in myelin, and the frontopontile tract appeared most involved.

Thionine stains of the cerebral cortex revealed that the changes in the atrophic gyri consisted of a notable diminution of cells in all layers, especially in the third layer; cells that remained appeared sclerosed or quite normal. Swollen cells were infrequently seen.

In the subcortical nuclear masses the changes were variable. In the entire caudate complex few nerve cells remained; of these, most were sclerosed, although occasional normal-appearing neurons were seen. In the globus pallidus and the subthalamic nucleus the nerve cells were greatly diminished in number, and the most frequent change consisted of swelling of the cytoplasm, with lipochrome pigments, absence of Nissl granules and displacement of the nucleus to one side (fig. 4 *A*). The large and small nerve cells of the putamen were normal in appearance and number. In the substantia nigra the number of cells was greatly diminished, but the few that remained appeared normal. Large quantities of melanin were seen scattered and lying free in the parenchyma (fig. 4 *B*).

In the red nucleus, the thalamus and the pulvinar, large quantities of lipochromes were observed in the cytoplasm of the nerve cells. Similar deposits were seen in the inferior olives, the pontile nuclei and the nuclei of the cranial nerve. It should be emphasized that in Pal-Weigert stains the lipochromes in these nuclear masses, as well as in the globus pallidus and the subthalamic nucleus, did not stain black, as do the nerve cells in cases of amaurotic family idiocy. The cerebellum revealed diminution in Purkinje cells and hypertrophy of the glia in Bergmann's layer. The blood vessels throughout the brain showed no changes that would not normally be seen in a person of the patient's age.

<div align="center">COMMENT</div>

Clinical Features.—The masked facies, the cogwheel rigidity and a certain amount of propulsion in the gait suggested the possibility of an early parkinsonian syndrome, but the associated profound dementia made this diagnosis untenable. Dementia paralytica was ruled out by laboratory studies. The final diagnosis was Pick's or Alzheimer's disease. In spite of numerous contributions to the differential diagnosis of those two diseases on clinical signs alone, it is quite impossible to make such a diagnosis unless the results of biopsy and encephalographic studies are utilized.

The occurrence of bilateral forced innervation late in the course of the disease suggests that area 6 of the frontal lobe was involved bilaterally (Adie and Critchley[1]; Richter and Hines[2]). However, forced innervation and forced grasping and groping occur frequently in severely demented patients and when present bilaterally have little, if any, localizing value. The presence of the sucking reflex is. I believe, merely the result of the profound retrogression in behavior and had no localizing value in this case at least. Stern,[3] in his study of a patient with severe organic dementia associated with sucking and grasping phenomena, observed at autopsy a unique selective degeneration of the thalamus bilaterally. This sucking reflex, as is the case of bilateral forced grasping and groping, may be merely the manifestation of a profound organic mental deterioration.

Pathologic Features.—The cortical atrophy was typical in nature and distribution of that associated with Pick's disease. However, the changes were not limited to the cortex alone but involved diffusely the entire brain in varying degrees. This is in agreement with the observations of Hassin and Levitin[4] and of Edwards and Swan.[5]

1. Adie, W. J., and Critchley, M.: Forced Grasping and Groping, Brain **50**:142, 1927.

2. Richter, C. P., and Hines, M.: The Production of the "Grasp Reflex" in Adult Macaques by Experimental Frontal Lobe Lesions, A. Research Nerv. & Ment. Dis., Proc. **13**:211, 1934.

3. Stern, K.: Severe Dementia Associated with Bilateral Symmetrical Degeneration of Thalami, Brain **62**:157, 1939.

4. Hassin, G. B., and Levitin, D.: Pick's Disease: Clinicopathologic Study and Report of a Case, Arch. Neurol. & Psychiat. **45**:814 (May) 1941.

5. Edwards, K. F., and Swan, C.: A Case of Pick's Cerebral Atrophy, M. J. Australia **2**:145, 1942.

The atrophy of the caudate nucleus was greater than in any case hitherto reported in the literature. Of all the subcortical gray masses, the caudate nucleus appears to be most frequently involved (Edwards and Swan,[5] Jansen [case 2],[6] Löwenberg [case 4],[7] Onari and Spatz,[8] Ley and associates [9] and von Braunmühl [several collected cases] [10]). Other investigators have described changes in other parts of the subcortical gray masses; Gullain and associates [11] reported a case with involvement of the olives and the globus pallidus, and van Bogaert [12] noted lesions in the pallidum and in the region of the corpus Luysi (subthalamic nucleus), which he asserted produced choreoathetosis during life. Giljarowsky [13] and Verhaart [14] observed changes in the cerebellum and pons. It is possible that the case of Stern [3] may be included in this broader concept of Pick's disease.

In view of the extensive changes in the cortex and the subcortical gray masses it is difficult, in fact impossible, to correlate the parkinsonian syndrome and the anatomic changes. The oldest changes in the subcortical gray masses were those in the caudate nucleus; more recent changes occurred in the substantia nigra, and the most recent changes were observed in the globus pallidus and the subthalamic nucleus. This suggests that the lesion in the caudate nucleus was the basis of the cogwheel rigidity, the rigid facies, the tremor and the propulsive gait observed in the patient three years before death. It should be emphasized, however, that Browder and Meyers [15] extirpated the head of the caudate nucleus for relief of postencephalitic tremors with good results. The various hypotheses concerning the anatomic basis of these syndromes of the extrapyramidal tracts, as advanced by Walshe,[16] Jakob [17] and the Vogts,[18] show that to date knowledge of these disorders is extremely meager.

Two types of changes in the nerve cells were seen in this case. In the frontal lobe and the caudate nucleus the cells appeared sclerosed; these regions were probably the first to be affected, and the picture suggests a completed pathologic

6. Jansen, J.: Ueber anatomische Veränderungen bei der Pickschen Krankheit, Acta psychiat. et neurol. 13:631, 1938.

7. Löwenberg, K.: Pick's Disease: Clinicopathologic Contribution, Arch. Neurol. & Psychiat. 36:768 (Oct.) 1936.

8. Onari, K., and Spatz, H.: Anatomische Beiträge zur Lehre von der Pickschen umschriebenen Grosshirnrindenatrophie (Pickschen Krankheit), Ztschr. f. d. ges. Neurol. u. Psychiat. 101:470, 1926.

9. Ley, J.; Titeca, J.; Divry, P., and Moreau, M.: Atrophie de Pick: Etude anatomo-clinique, J. belge de neurol. et de psychiat. 34:285, 1934.

10. von Braunmühl, A.: Ueber Stammganglienveränderungen bei Pickscher Krankheit, Ztschr. f. d. ges. Neurol. u. Psychiat. 124:214, 1930; Picksche Krankheit, in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1930, vol. 11, pp. 673-715.

11. Guillain, G.; Bertrand, I., and Mollaret, P.: Considérations anatomo-cliniques sur un cas de maladie de Pick, Ann. de méd. 36:249, 1934.

12. van Bogaert, L.: Syndrome extrapyramidal au cours d'une maladie de Pick, J. belge de neurol. et de psychiat. 34:315, 1934.

13. Giljarowsky, W.: Zur Pathologie der Rückentwicklungsprozesse, Ztschr. f. d. ges. Neurol. u. Psychiat. 139:509, 1932.

14. Verhaart, W. J. C.: Over die ziekte von Peck, Nederl. tijdschr. v. geneesk. 74:5586, 1930.

15. Browder, E. J., and Meyers, R.: A Surgical Procedure for Postencephalitic Tremors, Tr. Am. Neurol. A. 66:176, 1940.

16. Walshe, F. M. R.: Oliver-Sharpley Lectures on the Physiological Analysis of Some Clinically Observed Disorders of Movement, Lancet 2:405, 1929; Observations on the Nature of the Muscular Rigidity of Paralysis Agitans and on Its Relationship to Tremor, Brain 47:159, 1924.

17. Jakob, A.: The Anatomy, Clinical Syndromes and Physiology of the Extrapyramidal System, Arch. Neurol. & Psychiat. 13:596 (May) 1925.

18. Vogt, C., and Vogt, O.: Zur Lehre der Erkrankungen der striären Systeme, J. f. Psychol. u. Neurol. 25:627, 1920.

process. In the globus pallidus and the subthalamic nucleus the diseased nerve cells were swollen and filled with lipochromes; these changes are suggestive of a more acute degenerative process. It is also possible that the presence of iron in large quantities in the globus pallidus and the subthalamic nucleus, in contrast to the small amount in the cortex and its absence in the caudate nucleus, indicates a chronologic difference in the occurrence or the activity of the lesions. The distribution of the iron chiefly in the oligodendrocytes, the astrocytes and the nerve cells indicates that the process was degenerative rather than inflammatory (Metz [19]). The topographic distribution of the iron deposits can be correlated to a slight degree with the results of studies on normal brains by Guizetti, Spatz and others (Hernandez [20]). According to these workers, the globus pallidus (especially the oral portion) and the substantia nigra (especially the zona reticularis) are most abundant in iron, and the striatum and the subthalamic nucleus belong to the second group of iron-containing centers. The cerebral and cerebellar cortex normally contain much less iron than the structures just mentioned.

Efforts, especially by Onari and Spatz,[5] have been made in the past to explain the elective involvement of the central nervous system in Pick's disease on the basis of Edinger's theory that in all system degenerations which are due to "abiotrophy" the process affects the more recent structures exclusively. No confirmation of this hypothesis is found in this case. The caudate nucleus, belonging to the neostriatum, was almost completely destroyed; the globus pallidus, which is phylogenetically much older, was severely involved, and yet the putamen was fairly well preserved. According to the Vogts,[18] there is practically no difference in structure and origin between the caudate nucleus and the putamen.

It is doubtful whether the changes in the caudate nucleus and the pallidum are a result of retrograde degenerative changes secondary to the cortical involvement. In many cases with severe cortical involvement reported in the literature no changes in the basal ganglia have been present. In monkeys, Mettler [21] observed degenerated fibers to the caudate nucleus, globus pallidus, substantia nigra and subthalamic nucleus after unilateral ablations of area 9, and Hirasawa and Kato [22] noted degenerated corticofugal fibers to the head of the caudate nucleus, putamen, globus pallidus and substantia nigra after cauterization of areas 8 (a, β. γ. δ) and 9 (c, d). However, in man, no evidence has been presented to indicate direct fiber connections between the cortex and the striatum and pallidum (Vogts [18]).

SUMMARY AND CONCLUSION

In a clinicopathologic study of a case of Pick's disease extensive bilateral involvement of the caudate nucleus, the substantia nigra, the pallidum and the subthalamic nucleus was observed.

260 Crittenden Boulevard.

19. Metz, A.: Die drei Gliazellarten und der Eisenstoffwechsel, Ztschr. f. d. ges. Neurol. u. Psychiat. **100**:428, 1926.

20. Hernandez, R.: Iron Content of the Brain (Its Normal and Pathological Occurrence), Psychiatric Quart. **5**:95, 1931.

21. Mettler, F. A.: Corticofugal Fiber Connections of the Cortex of Macaca Mulatta: The Frontal Region, J. Comp. Neurol. **61**:509, 1935.

22. Hirasawa, K., and Kato, K.: Ueber die Fasern, insbesondere die corticalen extrapyramidalen aus den Areae 8 (a, β, γ, δ) und 9 (c, d) der Grosshirnrinde beim Affen, Folia anat. japon. **13**:189, 1935.

AGENESIS OF THE CORPUS CALLOSUM WITH POSSIBLE PORENCEPHALY

REVIEW OF THE LITERATURE AND REPORT OF A CASE

ALEXANDER T. BUNTS, M.D.

Associate Neurosurgeon, Cleveland Clinic

CLEVELAND

AND

LIEUTENANT JOHN S. CHAFFEE*

MEDICAL CORPS, ARMY AIR FORCES

The accumulation of reported data from twenty-five years of pneumoencephalographic studies has directed the interest of neurosurgeons to certain rare anomalous conditions of the brain which may be demonstrated in the encephalogram. These include agenesis of the corpus callosum, porencephalic cysts and cysts of the cavum septi pellucidi and the cavum Vergae. Interesting as these lesions are from a morphologic and a diagnostic standpoint, their study may be especially important because of the possibility that some abnormalities of mental and physical development, hitherto attributed to birth injury, may originate in embryonic or developmental defects of the brain. In this paper are reviewed all the reported cases in the English literature in which an antemortem diagnosis of agenesis of the corpus callosum was made. An additional case associated with a suspected porencephalic cyst is reported. Cysts of the cavum septi pellucidi and the cavum Vergae are discussed under "Differential Diagnosis."

HISTORICAL REVIEW

The first case of agenesis of the corpus callosum was reported by Reil[1] in 1812. In this, and in 81 other cases collected from the literature up to 1933 by Baker and Graves,[2] the condition was encountered incidentally at autopsy, only 2 of these being in the United States. In spite of the facility of ventriculography and encephalography since 1918 (Dandy[3]), not until 1934 did Davidoff and Dyke[4] report the first case of agenesis of the corpus callosum seen in a living patient by encephalography. The encephalogram in the first of 3 cases was interpreted as showing a cyst of the cavum septi pellucidi, and at autopsy, after a craniotomy, complete agenesis of the corpus callosum was noted. Likewise, in the first of 5 cases reviewed by Hyndman and Penfield[5] partial agenesis of the corpus callosum was discovered at operation in a case in which a cyst of the cavum septi pellucidi was suspected.

1. Reil, J.: Mangel des mittleren und freien Theils des Balkens in Menschengehirn, Arch. f. d. ges. Physiol. 11:341, 1812.

2. Baker, R., and Graves, G.: Partial Agenesis of the Corpus Callosum, Arch. Neurol. & Psychiat. 29:1054 (May) 1933.

3. Dandy, W. E.: Ventriculography, Ann. Surg. 68:5, 1918.

4. Davidoff, L. M., and Dyke, C. G.: Agenesis of the Corpus Callosum: Its Diagnosis by Encephalography; Report of Three Cases, Am. J. Roentgenol. 32:1 (July) 1934.

5. Hyndman, O. R., and Penfield, W.: Agenesis of the Corpus Callosum: Its Recognition by Ventriculography, Arch. Neurol. & Psychiat. 37:1251 (June) 1937.

EMBRYOLOGY

In the human fetus the corpus callosum develops between the third and the fifth month (fig. 1). The lamina terminalis connects the bilaterally expanding cerebral hemispheres. Emerging as a thickening of the lamina terminalis are the structures which later bridge the hemispheres, namely, the corpus callosum, the hippocampal commissures of the fornices and the anterior commissure. They grow together dorsally over the thalamus to form eventually a broad decussating band. The portion of the lamina terminalis forming the septum between the corpus callosum and the fornix becomes hollow from stretching and is known as
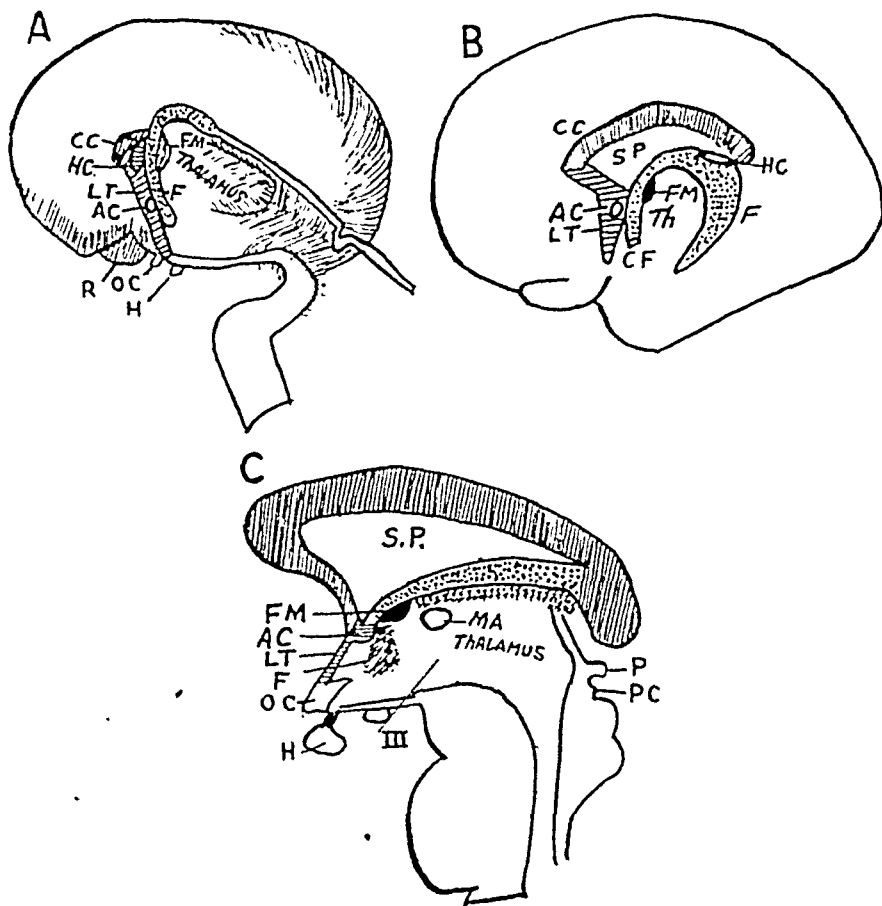
Fig. 1.—Schematic representation of the development of the septum pellucidum and corpus callosum (modified from Ranson [Anatomy of the Nervous System, ed, 6, Philadelphia, W. B. Saunders Company, 1939] and Hyndman and Penfield [5]). *A*, at 3 months of age; *B*, at 5 months of age, and *C*, from an adult.

In this figure, *A. C.*, indicates anterior commissure; *C. C.*, the corpus callosum; *C. F.*, the columna fornices; *F*, fornix; *F. M.*, foramen of Monro; *H*, hypophysis; *H. C.*, hippocampal commissure; *L. T.*, lamina terminalis; *M. A.*, massa intermedia; III, third ventricle; *O. C.*, optic chiasm; *P.*, pineal body; *P. C.*, posterior commissure; *R*, rhinencephalon; *S. P.*, septum pellucidum, and *Th.*, thalamus.

the cavum septi pellucidi. It lies cephalad to the third ventricle. Any arrested development of the corpus callosum is usually associated with faulty development of contiguous structures. Apparently, the extent depending on the time of embryonic arrest, abnormalities vary from a small defect in the splenium to complete absence of the corpus callosum, septum pellucidum, lyra of the fornices

and anterior commissure. Complete absence of the corpus callosum was noted in over half the cases· here reviewed.

In determination of the stage in the embryonic process at which arrested development occurs, Bruce's [6] subdivision is generally recognized.

First three weeks: Complete absence of corpus callosum, when hemispheres and ventricular system are a single, undivided unit.

Four weeks through three months: Absence of corpus callosum and anterior commissure, but perfect division of cerebral hemispheres by longitudinal fissure.

During fourth month: Absence of corpus callosum; presence of anterior commissure.

End of fourth month: Presence of anterior commissure and genu of corpus callosum.

Lesser degrees of agenesis of the corpus callosum vary directly in proportion to the lateness of onset of arrested development.

ASSOCIATED ANOMALIES

On the basis of a modification of the list of Baker and Graves,[2] with additions by other authors, the following anomalies frequently associated with agenesis of the corpus callosum are presented:

1. Dilatation of the posterior horns of the lateral ventricles.

2. Failure of the calcarine and parieto-occipital fissure to join because of interposition of a superficial gyrus.

3. Absence of radial arrangement of the sulci on the medial aspect of the hemispheres. This development is similar to that of the brain of a fetus at 6 months.

4. Absence of the septum pellucidum and the hippocampal commissure associated with total agenesis of the corpus callosum. The septum pellucidum is present in cases of partial agenesis of the corpus callosum.

5. Association of absence of the corpus callosum with at least one other anomaly of the brain: (a) cranial nerve defects; (b) incomplete separation of the frontal lobes; (c) hydrocephalus; (d) enlarged anterior commissure; (e) porencephaly, and (f) arhinencephaly.

6. Rarity of associated bodily defects, including: (a) cleft palate; (b) harelip; (c) cryptorchism; (d) thoracic stomach, and (e) coloboma of optic nerve.

FUNCTION OF THE CORPUS CALLOSUM

Clinical histories of patients with agenesis of the corpus callosum are interesting in view of the extensive study which has been devoted to the function of the corpus callosum. Cameron [7] claimed that defects other than those of the corpus callosum are responsible for the clinical manifestations of patients with agenesis of the corpus callosum. Tilney [8] pointed out that the opossum does not possess a corpus callosum but apparently has a compensatory hypertrophy of the hippocampal structure. In a strain of house mice King and Keeler [9] observed agenesis of the corpus callosum,

6. Bruce, A.: On the Absence of the Corpus Callosum in the Human Brain with Description of a New Case, Brain **12**:171, 1890.

7. Cameron, J. L.: The Corpus Callosum: A Morphological and Clinical Study, Canad. M. A. J. **7**:609, 1917.

8. Tilney, F.: The Hippocampus and Its Relationship to the Corpus Callosum, J. Nerv. & Ment. Dis. **89**:433 (April) 1939.

9. King, L. S., and Keeler, C. E.: Absence of Corpus Callosum: A Hereditary Brain Anomaly of the House Mouse, Proc. Nat. Acad. Sc. **18**:525, 1932.

which was familial and was inherited as a unit character. Superficial examination of these mice with either partial or complete agenesis of the corpus callosum disclosed no distinguishing abnormalities. Spitzka [10] expressed the belief that a direct relation existed between the thickness of the corpus callosum and mental efficiency. Later Ashby and Stewart,[11] in a study of the brains of mentally defective persons and normal healthy adults, found no correlation between the size of the corpus callosum and the degree of intelligence. Although Alpers and Grant [12] described a clinical syndrome associated with tumor of the corpus callosum, Armitage and Meagher [13] stressed that such deductions are misleading because associated structures of the brain are invariably involved by such infiltrating lesions. Armitage and Meagher,[13] Cameron [7] and Dandy,[14] working independently, by either surgical section of the corpus callosum or clinical evaluation could attribute no function to the corpus callosum. Dandy noted no unusual results from dividing the corpus callosum along the entire anteroposterior extent. Pavlov,[15] however, demonstrated that afferent fibers gave off conditioned reflex fibers to the opposite hemisphere via the corpus callosum. With present knowledge we may conclude that except for the abolition of some conditioned reflex impulses, Bruce's [6] statement seems correct, namely, "that if the brain is otherwise well developed, absence of the corpus callosum does not necessarily produce any disturbance of motility, coordination, general or specific sensibility, reflexes, speech or intelligence."

ETIOLOGIC FACTORS

The causation of agenesis of the corpus callosum has never been conclusively determined. Chemical toxins, syphilis and virus and pyogenic infections have been incriminated, but proof is lacking. De Lange [16] and Cameron [7] differed in their opinions as to whether hydrocephalus is the cause or the result of agenesis of the corpus callosum. According to Cameron, hydrocephalus is more apparent than real, inasmuch as the corpus callosum normally forms the roof of the lateral ventricles. Whatever the causative factor, there has obviously been some degree of arrested development of the corpus callosum in every case.

. CLINICAL MANIFESTATIONS

In table 1 are detailed the important clinical observations in the 15 reported cases of agenesis of the corpus callosum diagnosed during the life of the patient by pneumoencephalography. The youngest patient was 6 months old, and the oldest patient, who is the subject of the present paper, was 39 years of age. The age incidence in cases in which autopsy was performed varied from birth to 73 years,

10. Spitzka, E. A.: A Study of the Brains of Six Eminent Scientists, Tr. Am. Philos. Soc. **21**:175, 1907.

11. Ashby, W. R., and Stewart, R. M.: Brain of Mental Defective: Study of Morphology in Its Relation to Intelligence; Corpus Callosum in Its Relation to Intelligence, J. Neurol. & Psychopath. **14**:217, 1934.

12. Alpers, B. J., and Grant, F. C.: The Clinical Syndrome of the Corpus Callosum, Arch. Neurol. & Psychiat. **25**:67 (Jan.) 1931.

13. Armitage, G., and Meagher, R.: Gliomas of the Corpus Callosum, Ztschr. f. d. ges. Neurol. u. Psychiat. **146**:454, 1933.

14. Dandy, W. E.: Operative Experience in Cases of Pineal Tumor, Arch. Surg. **33**:19 (July) 1936.

15. Pavlov, I.: Conditioned Reflexes: An Investigation of the Physiological Activity of the Cerebral Cortex, translated and edited by G. Anrep, London, Oxford University Press, 1927.

16. de Lange, C.: On Brains with Total and Partial Lack of the Corpus Callosum and on the Nature of the Longitudinal Callosal Bundle, J. Nerv. & Ment. Dis. **62**:449, 1925.

the anomaly in most instances having been noted in persons under 10 years of age. Apparently, sex was not a determinate factor (table 1). Feeblemindedness and convulsive seizures of varying degrees of severity were the most common symptoms of agenesis of the corpus callosum. Other, less constant, symptoms included spastic paraplegia, hyperreflexia, athetoid movements, the Babinski sign, strabismus and nystagmoid movements of the eyes. The spinal fluid pressure might or might not be elevated. There was no history of convulsions in 5 cases, and intelligence was apparently normal in 4 cases. Congenital or developmental physical anomalies were commonly associated with agenesis of the corpus callosum.

ROENTGENOGRAPHIC DIAGNOSIS

The criteria for the encephalographic diagnosis of agenesis of the corpus callosum, as originally established by Davidoff and Dyke,[4] are as follows: (1) marked separation of the lateral ventricles; (2) angular dorsal margins of the lateral ventricles (this corresponds to the bicornuate appearance mentioned by Hyndman and Penfield[5]); (3) concave mesial borders of the lateral ventricles; (4) dilatation of the caudal portions of the lateral ventricles; (5) elongation of the interventricular foramens; (6) dorsal extension and dilatation of the third ventricle, and (7) radial arrangement of the mesial cerebral sulci around the roof of the third ventricle and extension of these sulci through the zone usually occupied by the corpus callosum.

Diagrammatic representations of the results of air studies of the ventricles of the brain in reported cases of agenesis of the corpus callosum have been drawn to scale and are shown together in figure 2. One is particularly impressed with the variations in the size and shape of the lateral ventricles. The pointed dorsal margins of the lateral ventricles, giving an appearance often referred to as bicornuate, are not consistently present. Incomplete filling of the ventricles with air causes distortions (case 3). A cursory inspection of figure 2 shows obvious deviations from normal in all these cases, and for the most part these variations are similar. These pneumoencephalographic standards for the diagnosis of agenesis of the corpus callosum, as originated by Davidoff and Dyke,[4] have served as the pattern for subsequent diagnoses. No other cerebral lesion may be confused with this defect except, possibly, a communicating cyst of the cavum septi pellucidi.

PORENCEPHALY

The case reported here is one of agenesis of the corpus callosum with the possible association of porencephaly. This combination is indeed rare. Inasmuch as proof of the diagnosis is wanting, the evidence without a didactic discussion of the subject is presented. Reeves,[17] in 1939, reported the first case of porencephaly associated with agenesis of the corpus callosum diagnosed in a living patient by encephalographic means. The anomaly in the cases presented by Hyndman and Penfield[5] (case 4, table 2) may have been porencephaly in association with agenesis of the corpus callosum, although the specific diagnosis was not mentioned. At autopsy LeCount and Semerak[18] observed porencephaly in 2 of 4 brains with agenesis of the corpus callosum. These authors defined porencephaly as a defect in the cerebral or the cerebellar structure appearing as a cystlike communication

17. Reeves, D. L.: Congenital Defects of the Cranial Nerves: Associated Porencephaly and Agenesis of the Corpus Callosum Diagnosed by Ventriculography, Bull. Los Angeles Neurol. Soc. 4:184, 1939.

18. LeCount, E. R., and Semerak, C. B.: Porencephaly, Arch. Neurol. & Psychiat. 14:365 (Sept.) 1925.

TABLE 1.—*Summary of Clinical Aspects of Patients with Agenesis of the Corpus Callosum Diagnosed During Life*

Author	Case No. and Patient's Initials	Age and Sex	Type of Agenesis	History and Physical Findings	Intelligence	Congenital or Developmental Defects	Subsequent History
Davidoff and Dyke [4]	1 N. E.	6 yr. F	Complete	Left-sided Jacksonian convulsions, beginning at 3 years of age; left hemiparesis; sudden onset of latter at age of 2 years, with unconsciousness, vomiting and fever of 2 weeks' duration	High	Hypoplasia of left side of body; premature puberty	Diagnosis of cyst of cavum septi pellucidi by encephalogram. Craniotomy revealed cyst with colorless fluid. Patient died after operation. Complete agenesis of corpus callosum seen at autopsy
	2 E. R.	21 yr. M	Partial	Frontal headache once a month since age of 14 years; grand mal seizures, mostly on left side; ataxia in left arm; partial defect in left superior homonymous quadrant of visual field	....	....	Diagnosis of agenesis of corpus callosum; no operation
	3 M. S.	3 yr. F	......	Premature birth; grand mal convulsions, tending to start on right side; onset at age of 2 years, 4 months; no abnormal neurologic signs	Retarded	Physical retardation	Craniotomy after diagnosis of cyst of cavum septi pellucidi. Patient survived operation
Hyndman and Penfield [5]	4 N. M.	8 yr. F	Partial	Born after 48 hours' labor, forceps delivery; left handed; difficulty in sentence formation; right Jacksonian convulsions since 4 years of age; nystagmus upward and to left; slight internal squint of right eye; deviation of tongue to right; intention tremor in right hand; spinal fluid pressure 420 mm. water (sitting position)	Normal	None	Original diagnosis was cyst of cavum septi pellucidi. Craniotomy performed; no defect seen. Diagnosis made after experience with subsequent cases
	5 S. V.	18 mo. F	Partial	Normal birth; petit mal attacks since 6 months of age; no localizing signs; voluntary motion slow and athetoid; spinal fluid pressure normal	Retarded	High arched palate	Craniotomy revealed thin pia-arachnoid instead of corpus callosum and enlargement of lateral ventricles
	6 G. D.	21 yr. M	Partial	Forceps delivery at full term; normal childhood; patient failed in history and English, passed in science; patellar reflex greater on right than on left; right hemiparesis	Average	Extremities on left side better developed than those on right	Patient living when last reported on
	7 H. D.	2 yr. M	Complete	Normal birth at full term; no convulsions. Ventricular system displaced by 130 cc. of air	Retarded	Occiput flat; bossed frontal bones	....

40

	Author	Age/Sex	Agenesis	Clinical findings	Mental status	Associated malformations	Remarks
8	S. S.	5 yr. F	Partial	Normal delivery; petit mal attacks; no convulsions	Normal	None	....
9	Cass and Reeves [19]	9 mo. M	......	Normal delivery; nystagmus on upward and lateral gaze; patient refused to sit up; no interest in surroundings; no convulsions	Retarded	Flat occiput; bossed frontal bones	Authors believe this condition cannot be distinguished from communicating cyst of cavum septi pellucidi
10	Reeves [17]	6 mo. F	......	Convulsive seizures from 2 months of age; bilateral Babinski sign; blurred optic disks; spinal fluid pressure 375 mm. of water	Retarded	Coloboma of left optic nerve and pigmentary chorioidal degeneration	Youngest patient on record in whom agenesis was diagnosed by air studies. Porencephaly associated with agenesis of corpus callosum
11	Kunicki and Chorobski [31]	21 mo. M	Complete	Ataxic, aimless movements; bilateral Babinski sign; optic nerve atrophy; no convulsions	Retarded	Unilateral cryptorchism; hydrocephalic skull	Craniotomy revealed complete agenesis; death 9 hours after operation
12	Gowan and Master	19 mo.	......	Normal delivery; left Jacksonian convulsion; left hyperreflexia; head measured 46 cm. at 2½ months; left Babinski sign	Retarded	Occiput flat; eyes widely separated	....
13	Goldensohn and others [33] M. M.	11 yr. F	Partial	Normal delivery; generalized convulsions, both grand and petit mal; headaches; vertigo; temper tantrums; sexual precocity; enuresis; defective associated swing of left arm; dysdiadokokinesis on left; knee jerk increased on right; Babinski sign and internal strabismus on right; negative visual fields and fundi	I. Q. 80	....	Electroencephalogram revealed asynchronism of electrical activity between left and right hemispheres, particularly between occipital lobes; waves generally slow
14	Derbyshire and Evans [32] M. T.	6 yr. F	Partial	Normal delivery; generalized convulsions 3 months previous to admission; general hyperreflexia, hypertonicity and spasticity	Retarded	Bilateral clubfeet	Electroencephalogram revealed fairly good synchronization between left and right hemispheres except between two occipital lobes with patient's eyes open
15	Bunts and Chaffee C. H.	39 yr. M	Complete	Normal delivery; grand and petit mal seizures since age of 5 months; temporary forgetfulness for recent events; neurologic signs negative except for early edema of optic disk and concentric contraction for color and form in both visual fields, most marked on right; spinal fluid pressure 515 mm. of water with patient in sitting position; 192 cc. of spinal fluid removed	Normal	None	Possible associated porencephalic cyst. Intensity of convulsions diminished for 3 months after encephalographic study; electroencephalogram showed diffuse dysrhythmia, irregular slow waves, absence of normal alpha activity and synchronization between hemispheres except in the occipital regions when the patient's eyes were open

41
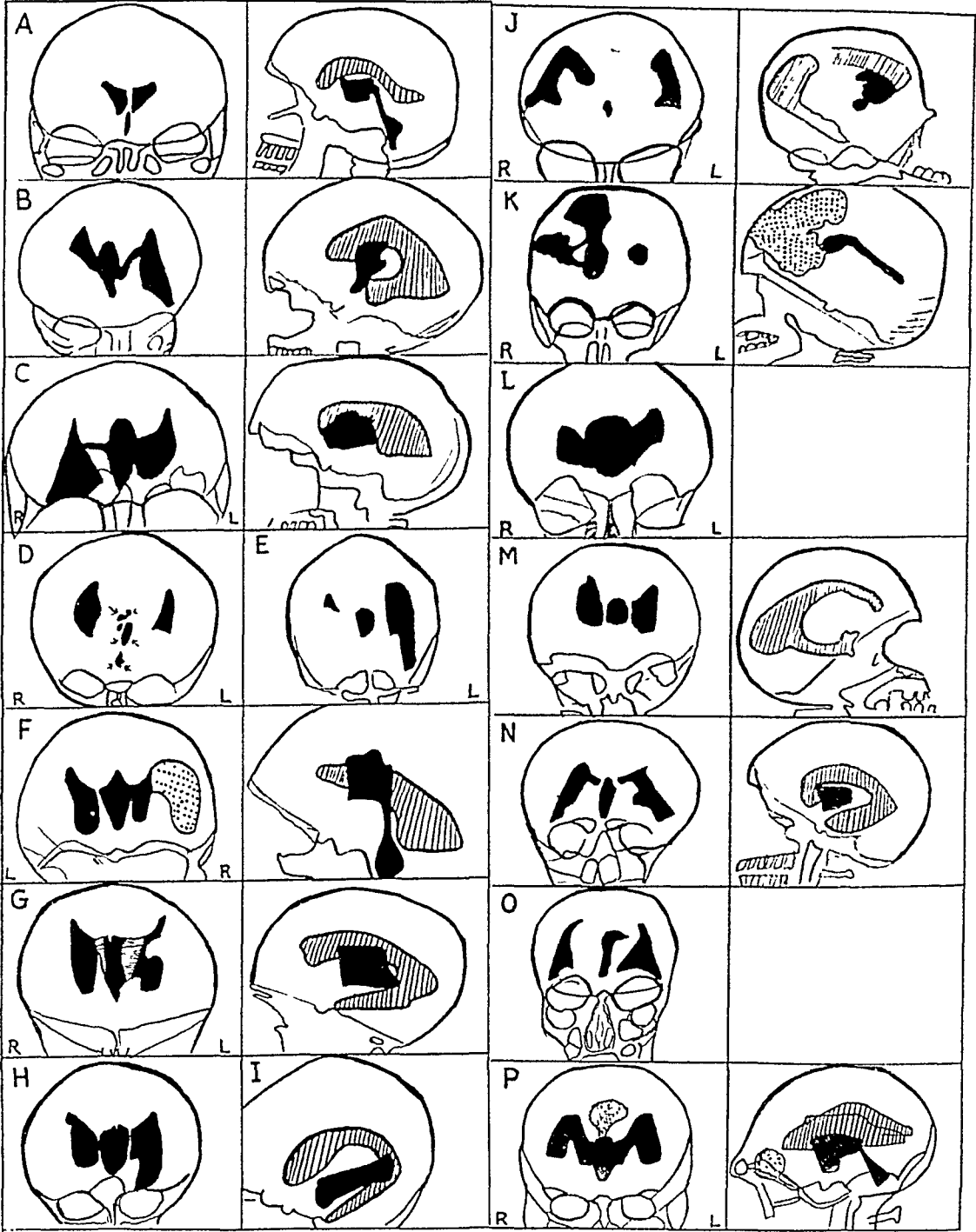
Figure 2

(See legend on opposite page)

with the ventricles, or separated from them by only a thin layer of brain tissue, covered on the outside by the pia-arachnoid and filled with a clear, colorless fluid. A case of porencephaly is diagrammatically illustrated in figure 3 B.

DIFFERENTIAL DIAGNOSIS

In the first cases of agenesis of the corpus callosum reported by Davidoff and Dyke[4] and Hyndman and Penfield[5] the condition was diagnosed as cyst of the

---

EXPLANATION OF FIGURE 2

Diagrammatic representation of cerebral air studies in reported cases of agenesis of the corpus callosum.

A, normal encephalogram.

B, (Davidoff and Dyke,[4] case 1), widely separated and dilated lateral ventricles, particularly the temporal horns and the posterior portions of the bodies. The third ventricle is high and dilated. The foramen of Monro is elongated.

C (Davidoff and Dyke,[1] case 2), widely separated and dilated lateral ventricles, particularly the posterior portions. The third ventricle is dilated and extends high. The foramen of Monro is elongated.

D (Davidoff and Dyke,[4] case 3), wide separation of the lateral ventricles. Arrows indicate the outline of the third ventricle, which is incompletely filled.

E (Hyndman and Penfield,[5] case 6), wide separation of the lateral ventricles; only partial filling of one ventricle; third ventricle high and dilated.

F (Hyndman and Penfield,[5] case 4), partial agenesis. Wide separation and dilatation of the lateral ventricles, particularly the posterior portions. The third ventricle rises high in the middle of the corpus callosum. Note the appearance of a possible porencephalic cyst associated with the right lateral ventricle.

G (Hyndman and Penfield,[5] case 5), partial agenesis. Dilatation and separation of the lateral ventricles; high extension of the third ventricle; indentation of the falx cerebri. Horizontal stippling indicates broadening of the third ventricle anterior to the optic thalamus.

H (Hyndman and Penfield,[6] case 7), complete agenesis. Dilatation and widening of the lateral ventricles; indentation of the falx on the cephalic aspect of the dilated third ventricle.

I (Hyndman and Penfield,[5] case 8), partial agenesis in the splenium. No evidence of agenesis anteriorly, in the anteroposterior roentgenogram.

J (Cass and Reeves,[19] case 9). The third ventricle is poorly shown in the anteroposterior view. In the right lateral view the third ventricle has a "cocked hat" appearance. Complete filling of the lateral ventricles not seen, although dilatation is present.

K (Reeves,[17] case 10), midline porencephalic cyst with agenesis of the corpus callosum. The right lateral view shows the cyst connected with the lateral ventricle. The author was undecided whether the cyst was connected with the third ventricle.

L (Kunicki and Chorobski,[31] case 11), complete agenesis; anteroposterior view only. The third ventricle is very wide, with consequent wide separation of the lateral ventricles and rises higher than the upper level of one lateral ventricle.

M (Gowan, L. R., and Masten, M. G.: Agenesis of the Corpus Callosum: Diagnosis of a Case by Encephalography, Am. J. Dis. Child. 60:1381 [Dec.] 1940; case 12), widely separated and dilated lateral ventricles, particularly the posterior portions, and pointed dorsal surfaces of the lateral ventricles. The third ventricle is not visualized in lateral view.

N (Goldensohn and others,[33] case 13), bicornuate, "bat wing" appearance of the lateral ventricles; elongation of the foramen of Monro; dilated, high third ventricle.

O (Derbyshire and Evans,[32] case 14), wide separation and dilatation of the lateral ventricles, with bicornuate appearance. The third ventricle is irregular and extends high between the lateral ventricles.

P (present case; case 15), widely separated and dilated lateral ventricles, with "bat wing" appearance; third ventricle dilated and high, its dome extending above the foramens of Monro. The dotted area outlines a possible associated porencephalic cyst.

TABLE 2.—*Encephalographic Evidence of Agenesis of Corpus Callosum*

Case	Lateral Ventricles			Foramen of Monro	Third Ventricle		
	Position	Shape	Size		Position	Shape	Size
1	Separated widely	Concave mesially; dorsal margins pointed	Posterior portion of bodies and temporal horns greatly enlarged; right frontal horn absent; left frontal horn rudimentary	Elongated; widened	Slightly to right of midline; between the lateral ventricles; top located 1.3 cm. dorsal to foramens of Monro	Somewhat triangular in anteroposterior view with base turned dorsally; "cocked hat" appearance from side	Enlarged; 1.0 cm. wide; 4.5 cm. high
2	Separated 4.3 cm.	Concave mesially; dorsal margins pointed	Frontal horns absent; posterior portions of bodies greatly dilated; temporal horns moderately dilated	Elongated; widened	Between lateral ventricles; separated from each lateral ventricle by 1 cm.; top 1.9 cm. dorsal to foramens of Monro	"Cocked hat" appearance from side	1.7 cm. wide; 4.7 cm. high; 5 cm. long
3	Separated 5 cm.	Concave mesially; dorsal margins pointed	Frontal horns narrow; posterior portions of bodies moderately dilated; temporal horns slightly dilated	Not seen	Between lateral ventricles; separated from the lateral ventricles by 1 cm. on left and 0.5 cm. on right	Incomplete filling with air gives appearance of isolated islands of air	1 cm. wide; 3.6 cm. high
4	Separated widely	Bicornuate or angular dorsal surfaces	Enlargement of posterior horns; cystic enlargement of body of left lateral ventricle, with appearance of porencephalic cyst	Elongated; widened	Central; between and almost as high as top of lateral ventricles	Angular cephalic end, rounded base; connection with cerebral aqueduct and fourth ventricle seen in lateral view	About six times normal size
5	Separated widely	Bicornuate	Enlargement of posterior horns	Elongated; widened	Central	Moniliform in anteroposterior view; superior aspect indented by falx cerebri; superior margin horizontal in lateral view	About four times normal size
6	Separated widely	Convexity of mesial borders	Left ventricle larger than right, left indicating atrophy of hemisphere; enlargement of posterior horns	Not seen	Central and high	Wide with rounded apex	About three times normal size
7	Wide	Symmetric; bicornuate	Posterior horns greatly enlarged	Not seen	Central; several centimeters higher than normal	Ovoid; impression of falx on superior surface	About six times normal size

44

8	Defect in splenium not seen in postero-anterior view	Symmetric; bicornuate	Slightly enlarged	········	Central; posterior portion above and posterior to upper end of cerebral aqueduct; agenesis in splenium of corpus callosum	Posterior part like tail	Normal anteriorly; wider posteriorly
9	Separated widely	Anterior horns normal; concave mesial margin of right ventricle; lacks bicornuate appearance	Hydrocephalus, involving especially posterior horns	Not seen	Central and high	"Cocked hat" appearance on lateral view	3.5 by 0.6 cm.
10	Separated widely	Indistinct; blended with porencephalic cyst on right	Not enlarged except as right ventricle blends with cyst	Not seen	Central and high; appears to continue into porencephalic cyst	Normal	Author undecided whether continuous with porencephalic cyst
11	Separated widely	Elongated; upper poles inclined outward; rounded dorsal surfaces	Enlarged	Not seen	Central; high as top of lateral ventricle	Domelike roof	Tremendous width
12	Separated widely	Concave mesial borders; pointed dorsal surfaces	Two and a half times normal	Not seen	Central and high	Moniliform; not visualized in lateral view	2.3 by 1.3 cm. in anteroposterior view
13	Wide separation of posterior horns	Bicornuate; "bat wing" appearance	Dilated posterior horns	Elongated; widened	Central and high	Moniliform in anteroposterior view	Dilated
14	Wide separation of posterior horns	Bicornuate; pointed dorsal surfaces	Dilated	Not seen	Central and high; no lateral view submitted	Irregular; vertical; elongated	Elongated about five times normal size
15	Wide separation, particularly of posterior horns	"Bat wing" appearance; rounded cephalad; concave mesial borders	Greatly dilated body and posterior horns	Elongated; widened	Central and high; top rises above foramen of Monro	Moniliform; "cocked hat" appearance in lateral view	3 by 2 cm.

45

cavum septi pellucidi. Recently Cass and Reeves [19] (case 9) stated that in their case the lesion could not surely be differentiated from cyst of the cavum septi pellucidi. A careful analysis of the pathologic anatomy applied to encephalographic interpretation in most instances will establish a differential diagnosis of agenesis of the corpus callosum and cyst of the cavum septi pellucidi (fifth ventricle) and of the cavum Vergae (sixth ventricle). A cavity within the septum pellucidum occurs much more commonly than is generally appreciated and is seen in almost all infants. Van Wagenen and Aird [20] reported that of 30 consecutive brains examined at the University of Rochester School of Medicine, 18, or 60 per cent. had some dilatation of the cavity of the septum pellucidum.

The cavum septi pellucidi and the cavum Vergae normally are not in communication with the ventricular system, are not lined by ependymal cells and do not contain tela choroidea. Conjectures as to why they happen to contain fluid have been best discussed by Van Wagenen and Aird [20] and by Wolf and Bamford.[21] The cavum Vergae is really the posterior extension of the cavum septi pellucidi,
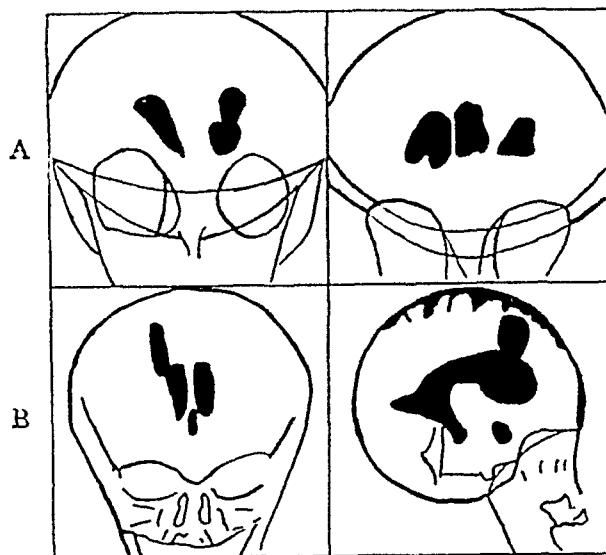
Fig. 3.—Diagrams representing the two conditions which must be differentiated from agenesis of the corpus callosum.

Above, on the left is the ventriculogram of a noncommunicating cyst of the cavum septi pellucidum before rupture, showing dilatation of the lateral ventricles and absence of a central air shadow between them. On the right the central air shadow appears after artificial communication was setablished between the cyst and the ventricle. (From Dandy,[22] page 58; a boy aged 4½ years.)

Below, an anteroposterior and a lateral view of a porencephalic cyst in communication with the right lateral ventricle. The ventricles are slightly dilated but not separated, and the third ventricle is in normal position. (From Reavis, C. W., and Kilby, W. L.: Porencephaly, Bull. School Med. Univ. Maryland **26:**190 [Jan.] 1942; a girl aged .14 months.)

and although the two cavities may be separated by the pillars of the fornix, when dilated they usually communicate with each other through a small defect in the

19. Cass, A. B., and Reeves, D. L.: Partial Agenesis of the Corpus Callosum: Diagnosis by Ventriculographic Examination, Arch. Surg. **39:**667 (Oct.) 1939.

20. Van Wagenen, W. P., and Aird, R. B.: Dilatations of the Cavity of the Septum Pellucidum and Cavum Vergae, Am. J. Cancer **20:**539, 1934.

21. Wolf, A.. and Bamford, T. E.: Cavum Septi Pellucidi and Cavum Vergae, Bull. Neurol. Inst. New York **4:**294, 1935.

fornix (fig. 4). The two cavities are bounded anteriorly, superiorly and posteriorly by the corpus callosum, laterally by the walls of the septum pellucidum and inferiorly by the rostrum of the corpus callosum and the lamina rostralis (fig. 4). The cavum septi pellucidi and the cavum Vergae are superior to the third ventricle, being on the same level with, and forming the mesial walls of, the lateral ventricles (fig. 4 C). A considerable portion of the septum pellucidum lies anterior to the third ventricle. Therefore the third ventricle is normally inferior to the cavum septi pellucidi and the cavum Vergae, being separated from them by the body of the fornix with its underlying tela choroidea. Furthermore, the third ventricle is beneath the level of the bodies of the lateral ventricles.

Dandy,[22] citing Verga, pointed out cysts of the cavum septi pellucidi and cavum Vergae, and Van Wagenen and Aird[20] classified them as follows: (1) Noncommunicating cyst, which is a closed intact cavity (fig. 3 A, on left); (2) communicating cyst, in which a communication with the third or the lateral ventricles has been established as a result of rupture of the walls due to differences in fluid pressure between the cyst and a ventricle (appearance similar to that in figure 3 A, on right), and (3) secondary or acquired cyst, in which communicating dilatations are present as a part of later developing, or superimposed, hydrocephalus.

The literature as far back as Verga contains many reports on specimens of cysts of the cavum septi pellucidi and the cavum Vergae. The reports of Dandy,[22] Van Wagenen and Aird,[20] Berkwitz,[23] Leslie[24] and Turnbull,[25] constituting a reasonable search of the English literature, revealed only 16 cases in which the pneumoencephalographic diagnosis of cyst of the cavum septi pellucidi or the cavum Vergae was made. In 5 of these cases the cyst was of the air-containing, communicating type and was diagnosed as such in conjunction with some other pathologic lesion in the brain, such as tumor or arachnoiditis, which accounted for the symptoms of the patient. In 11 cases the cyst was noncommunicating and therefore did not contain air on encephalographic examination, and in each instance the cyst was the only lesion to account for the symptoms. In 10 of these 11 cases of noncommunicating cyst of the cavum septi pellucidi or cavum Vergae, cure was effected when a communication between the cyst and the lateral ventricle was established, by operation, as in the cases of Dandy,[22] Van Wagenen and Aird,[20] Leslie,[24] Tönnis[26] and Kötter,[27] by spontaneous rupture of the cyst wall coincident with changes in pressure during the encephalographic procedure, as reported by Van Wagenen and Aird,[20] Berkwitz,[23] Turnbull[25] and Stookey,[28] or by aspiration of the cyst, as mentioned by Spurling and Jelsma.[29] Evidence of a sudden transition from a symptom-producing, noncommunicating cyst to a symptomless, communicating cyst as a result of spontaneous rupture of the cyst wall is given in the case reported by Van Wagenen and Aird[20] and by Laubenthal.[30]

22. Dandy, W.: Congenital Cerebral Cysts of the Cavum Septi Pellucidi (Fifth Ventricle) and Cavum Vergae (Sixth Ventricle), Arch. Neurol. & Psychiat. **25**:44 (Jan.) 1931.

23. Berkwitz, N. J.: Noncommunicating Cyst of the Septum Pellucidum, Minnesota Med. **22**:402, 1939.

24. Leslie, W.: Cyst of the Cavum Vergae, Canad. M. A. J. **43**:433, 1940.

25. Turnbull, F.: Cyst of the Septum Pellucidum and Epilepsy, Bull. Vancouver M. A. **15**:183, 1939.

26. Tönnis, W.: Kongenitale Cyste des Septum pellucidum, Zentralbl. f. Chir. **62**:1018, 1935.

27. Kötter, E.: Ueber das Cavum septi pellucidi und andere Veränderungen des Septum Pellucidum, Nervenarzt **9**:392, 1936; cited by Laubenthal.[30]

28. Stookey, cited by Van Wagenen and Aird.[20]

29. Spurling, R. G., and Jelsma, F., cited by Van Wagenen and Aird.[20]

30. Laubenthal, F.: Ueber Veränderungen des Septum pellucidum, Nervenarzt **10**:401, 1937.

Many postmortem specimens exist in which the communicating type of cyst of the cavum septi pellucidi and cavum Vergae was present without symptoms or in conjunction with other lesions to account for the symptoms. Although there are available even a greater number of specimens of small, noncommunicating cysts
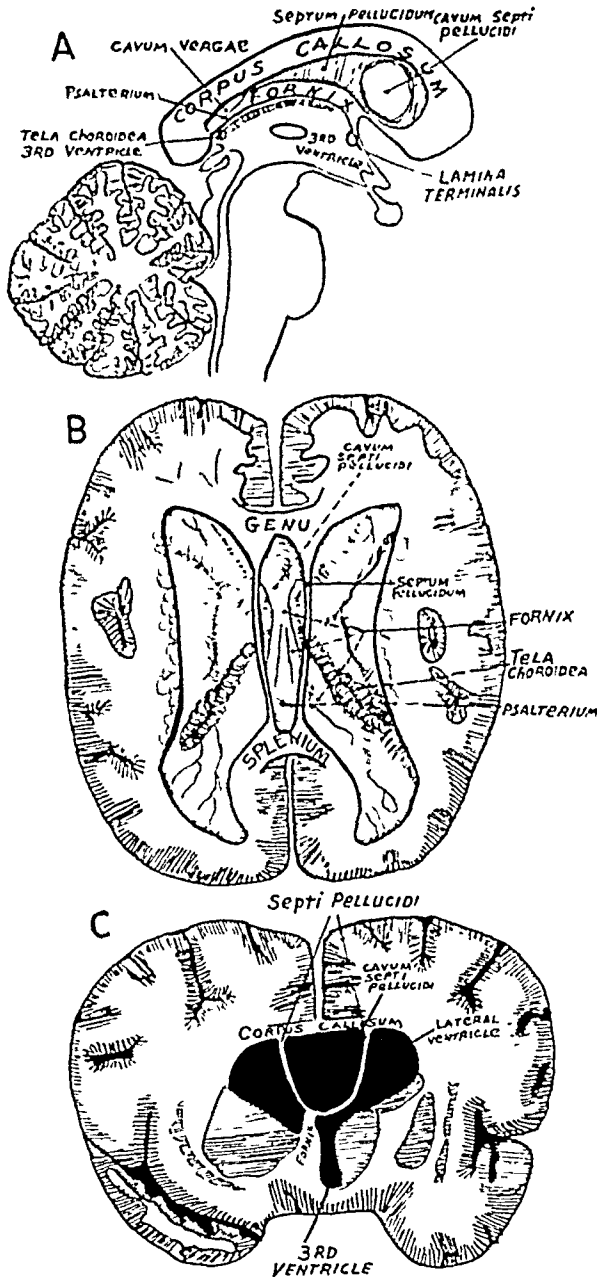
Fig. 4.—*A*, sagittal view, showing small cavum Vergae separated from the cavum septi pellucidi by a slender partition of fornix. (Diagram after Dandy,[22] page 48.)

B, large cavity formed by union of cavum septi pellucidi and the cavum Vergae. (Diagram after Dandy,[22] page 49.)

C, position of noncommunicating cyst of the cavum septi pellucidi in relation to the ventricular system. (Diagram after Dandy,[22] page 48.)

of the cavum septi pellucidi and cavum Vergae which produced no symptoms, the larger cysts are invariably associated with neurologic signs or symptoms. This

is an important and logical point in differential diagnosis, inasmuch as the cyst should exert no pressure if it is in free communication with the ventricular system.

The following pneumoencephalographic features in the differential diagnosis of cyst of the cavum septi pellucidi and agenesis of the corpus callosum are taken largely from the thesis of Kunicki and Chorobski,[31] with additions by us.

A.   Noncommunicating, fluid-filled cyst of the cavum septi pellucidi.

1.   The anterior horn and the body of the lateral ventricles may or may not be separated. Their mesial walls may be merely invaginated, without separation.

2.   There is no central shadow of air between the lateral ventricles (fig. 3 A).

3.   The third ventricle cannot rise to the height present in cases of agenesis of the corpus callosum because the cyst of the cavum septi pellucidi prevents its ascent.

4.   In an encephalographic examination, pressure of the cyst of the cavum septi pellucidi on the foramen of Monro might prevent drainage of the lateral ventricles. which therefore would not be visualized (fig. 4 C).

B.   Communicating cyst of the cavum septi pellucidi.

1.   The lateral ventricles are not separated and do not have a filling defect in their mesial walls.

2.   No enlargement of the cyst or the ventricles is present, unless as a part of general hydrocephalus.

C.   Cyst of the cavum septi pellucidi communicating with one lateral ventricle.

The shadows of air in the lateral ventricles will approach each other in the midline, the separating, unperforated wall of the cavum either being vertical or deviating from the ventricle containing air under a higher pressure toward the ventricle in which the pressure of air is lower.

REPORT OF CASE

History.—A single white man aged 39, the youngest of 7 children, was born after a normal uneventful labor, without recourse to instruments. There was no history of a resuscitation problem following birth or a feeding problem in the first five months of life. No abnormalities of physical or mental development were observed in early infancy. After a siege of severe diarrhea his first convulsion occurred at 5 months of age, coincident with sudden weaning at the time of his mother's death. The seizures, of a minute's duration, occurred once a month, were always nocturnal and were characterized by a generalized tonic and clonic convulsion and unconsciousness, without loss of sphincter or bladder control.

After the age of 20 years his seizures became generalized and tonic but invariably occurred in the daytime. The attacks were preceded by general irritability and an aura of nausea, right frontal headache and involuntary swallowing. If he was lying down before an attack he would rise to his feet, if he was standing he would kneel on his right knee. The seizures usually lasted about a minute. If not supported, he was apt to fall, and during one episode his clavicle was fractured. After an attack he frequently wandered about aimlessly in a disoriented manner, being able to open and close doors, and was silent and apparently oblivious to any one's addressing him. On his regaining insight and resuming his work, he suffered only a right frontal headache and recalled nothing of the spell except the aura.

Within two days of his vaccination for smallpox, at 6 years of age, he had about twenty generalized grand mal seizures, each of a minute's duration. In his opinion, periods of transient loss of memory followed this episode and have persisted up to the present. In school he had no particular difficulty in preparing or understanding his lessons. In the classroom, however, when he was called on to recite, he often forgot subject matter which he had memorized the night before. His humiliation was increased when after school the knowledge would return. Eventual retention of facts was normal. His grades were good in mathematics and grammar,

31. Kunicki, A., and Chorobski, J.: Ventriculographic Diagnosis of Agenesis of the Corpus Callosum, Arch. Neurol. & Psychiat. 43:139 (Jan.) 1940.

but he failed in history and geography. He stopped school after the seventh grade. He had been employed by a city illuminating company for twenty-three years. The company, fearing that he might be injured during a spell, transferred him from his former position as an expert linesman to that of a ground worker. Transient loss of memory had disturbed him. On many occasions he had forgotten orders and even had to return to his foreman to inquire about the nature of a task assigned to him. He stated that he sometimes staggered and seemed to be in a fog, when he could not recall instructions. He had been able to conceal the fact of his memory difficulty from his family up to the time of admission.

His sister related that she met him one evening at a railroad station and noted that he maintained a strange, blank facial expression while she drove him home. During this time he answered questions but offered no leading conversation. On their arriving home he could remember nothing of the journey with his sister.

The patient had a good disposition, was well liked by his friends, was intelligent and had a remarkably good insight into his own problem. He was, however, given to moods of depression concerning the futility of his life. He was hospitalized on Oct. 12, 1942 because of the increasing intensity of frontal headaches and convulsions during the preceding month.

Fig. 5.—Front and side views of C. H. (present case).

Medical History.—He had attacks of measles, mumps and chickenpox during childhood. A tonsillectomy was performed in 1930. The results of studies of the spinal fluid made at another institution in 1930 were reported to be normal.

Family History.—An older sister died at the age of 3 years, of "brain fever." She was well until two days before her death, when she had a convulsion, followed by prolonged coma.

General Examination.—The patient presented an average, normal appearance and seemed well nourished and well developed (fig. 5). Aside from poor teeth, no abnormalities were seen. Neurologic examination gave entirely negative results except for a suggestion of adiadokokinesis in the left hand. Examination of the visual fields revealed concentric contraction to form and color in both eyes, most marked in the left eye. Early edema of the optic disk of the right eye and definite edema of the disk of the left eye were present and were thought to be due to low grade or long-standing increased intracranial pressure.

Encephalographic Study.—An encephalographic test was made on Oct. 21, 1942. The initial pressure was 515 mm. of water, with the vertex level at 770 mm. The pressure rose to 595 mm. of water after the injection of 10 cc. of air; 192 cc. of spinal fluid was then removed, and 197 cc. of air was injected into the subarachnoid space. The report on the spinal fluid was as follows: The fluid was clear and contained no cells and no globulin; the total protein content measured 30 mg. per hundred cubic centimeters; the Wassermann and Kahn reactions were negative and the colloidal gold curve was normal.

The encephalogram (fig. 6) revealed no abnormalities of the skull. In the anteroposterior view the lateral ventricles were considerably dilated and widely separated and had a bat wing

appearance. In the lateral view the lateral ventricles were dilated, particularly in their posterior horns. In the anteroposterior view the third ventricle was dilated, measuring 2 by 3 cm. on the roentgenogram. Its location was higher than normal, and its dome rose well above the foramens of Monro. The characteristic appearance of the third ventricle, which has been referred to as that of a "cocked hat," was seen in the lateral exposure. The interventricular foramens were elongated and widely dilated. A definite, sharply demarcated area of diminished density was seen above the third ventricle and between the lateral ventricles in the posteroanterior view and was clearly localized in the frontal area in the lateral view. This area measured 3 by 4 cm. on the encephalogram and may have been a porencephalic cyst. Extending in tentacle-like fashion was a narrow, air-containing channel appearing as a bridge between the cyst and the third ventricle. Close stereoscopic examination, however, revealed that it was most probably a distorted mesial cerebral sulcus (indicated by *A*, fig. 6 C).
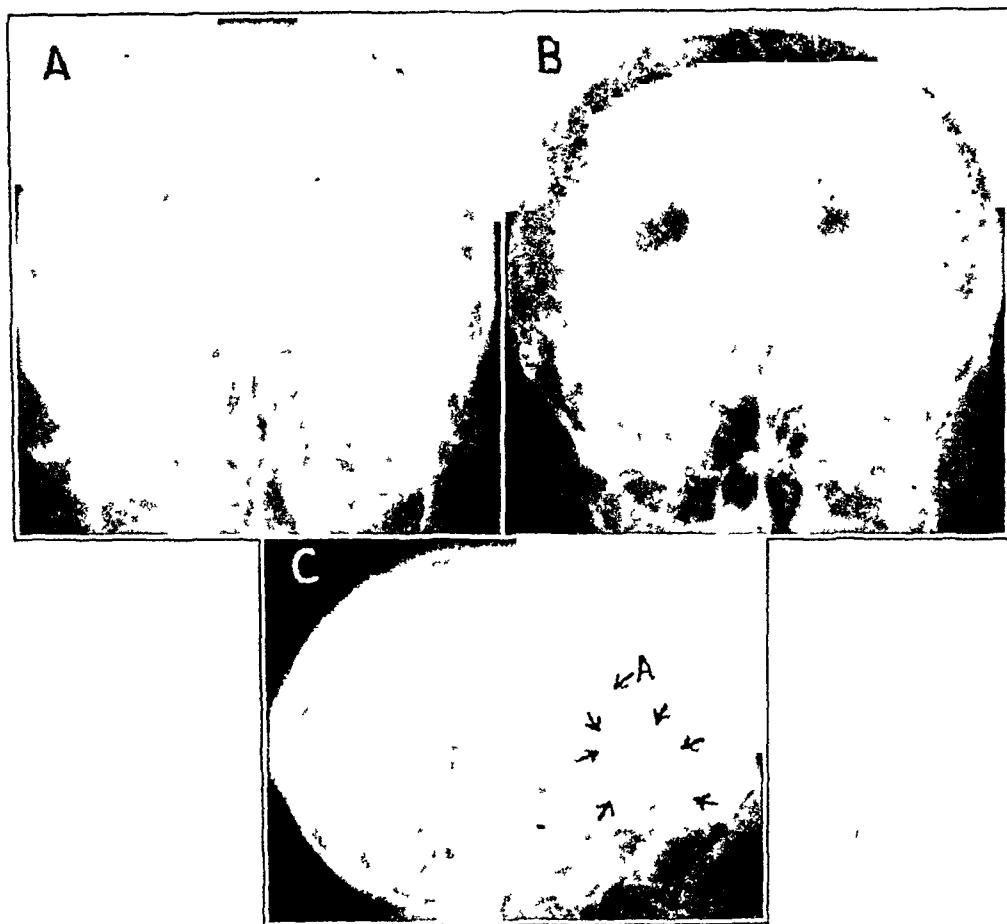
Fig. 6—Encephalograms in present case. *A*, posteroanterior and, *B*, anteroposterior view *C*, lateral view. Arrows denote periphery of a possible porencephalic cyst.

After the encephalographic examination the patient experienced severe headache, out of proportion to that usually following the procedure. Within five days this had subsided, and during the next month he was almost asymptomatic and had no convulsions. Within two months his seizures recurred and required sedation. After nine months the headaches were mild and infrequent. The convulsions, however, were similar to those before the examination but responded well to sedation therapy. An understanding of the clinical course is important in a differentiation of the lesion in this case from a noncommunicating cyst of the cavum septi pellucidi. Inasmuch as symptoms continued after encephalographic examination, it seems probable that this case was not one of noncommunicating cyst of the cavum septi pellucidi which ruptured spontaneously during the encephalographic procedure. Had this occurred the patient should have been relieved of his symptoms.

Electroencephalographic Study.—Bipolar recording was performed on Jan. 22, 1943; the monopolar method was used on March 18 by Dr. E M. Zucker, of Cleveland City Hospital, who also interpreted the tracings (fig. 7). With the bipolar method leads were taken from the frontal, precentral, postcentral and occipital regions, high and low along each side. Channel 1

was between the frontal and the precentral region; channel 2, between the precentral and the postcentral region, and channel 3, between the postcentral and the occipital region.

Low along the right side there was little alpha rhythm except in channel 3, where there were fairly constant 9 to 11 per second waves with an amplitude of about 20 microvolts. There was a rapid, low voltage (28 to 30 per second) rhythm in all leads. Several random slow waves of about 20 to 30 microvolts appeared in channel 1. High along the right side were numerous 3 to 4 second waves. In channel 3 there was fairly regular alpha rhythm.

High along the left side slow waves were frequently encountered in channel 1. In channel 2 little alpha activity was present, there being low voltage, fast waves not unlike beta activity. Again, channel 3 showed a dominant alpha rhythm. The activity in the three channels low along the left side was much the same as that high along the same side.

The transfrontal channels showed constant fast waves of low amplitude and irregular slow waves, especially from the channel across the midline and on the left side. The transprecentral channel was similar to the transfrontal channels, with beta waves and random slow waves predominant from the left side and across the midline. The transpostcentral channel showed some 9 to 11 per second waves, with superimposed beta activity. The transoccipital leads
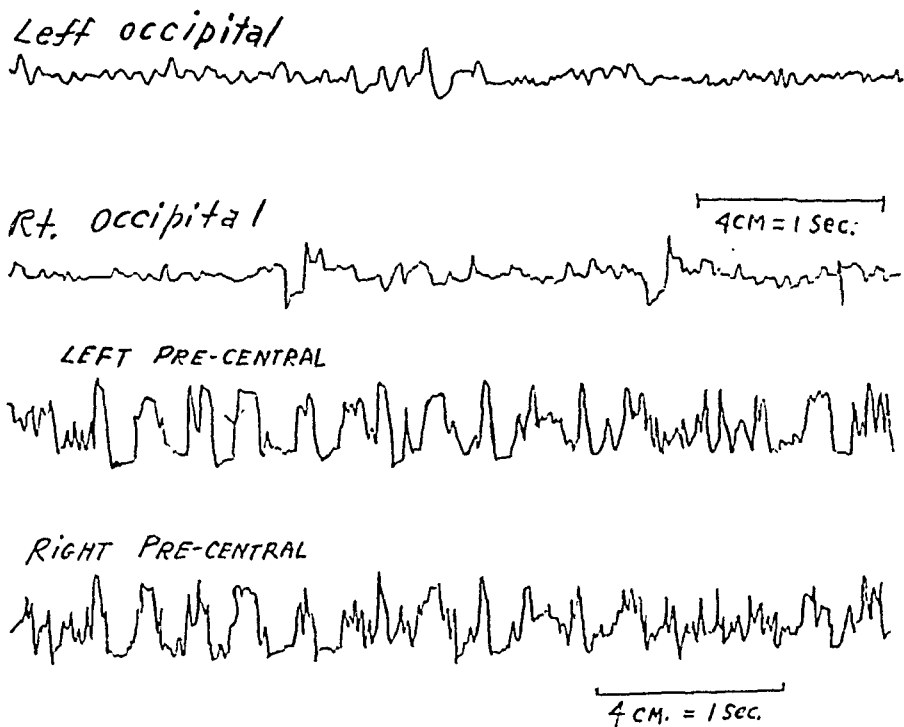
Fig. 7.—Monopolar method of recording brain waves by electroencephalography. Above: asynchronization of waves between the left and the right occipital lobe with the patient's eyes open. Note absence of normal alpha rhythm. Below: Fairly good synchronization between the left and the right precentral area.

showed fairly normal alpha waves from the right side and across the midline. The channel between the two occipital electrodes on the left side showed less alpha rhythm.

Monopolar recordings were made from the occipital, the postcentral, the precentral and the frontal region. *Simultaneous records were taken from corresponding areas of the two* sides. In records taken from the same side there was little difference between the frontal, the precentral, the postcentral and the occipital lead. There was definite dysrhythmia in all leads on both sides, more severe on the left. In a comparison of activities from the two sides in corresponding regions taken simultaneously, there appeared to be synchronization except in the record taken from the two occipital regions with the patient's eyes open.

Conclusion.—These electroencephalograms were definitely abnormal. They were characterized chiefly by irregular slow waves and absence of normal alpha activity. There was a continuous diffuse dysrhythmia, somewhat more severe on

the left. No phase reversal was observed in the bipolar method which could be used to localize definitely a cortical defect. With the monopolar recording there appeared to be good synchronization between the two sides except between the two occipital regions when the eyes were open.

This is the third case of agenesis of the corpus callosum on record in which electroencephalographic tracings have been made. Discussions of the electroencephalographic pattern in cases of agenesis of the corpus callosum reported independently in 1941 by Derbyshire and Evans [32] and by Goldensohn and associates [33] offer a few points for comparison with the tracings in this case. Derbyshire and Evans found instability of alpha rhythm similar to that in the tracing here reported. They also observed another point of similarity in that synchronization between the hemispheres was fairly good except between the occipital lobes. These authors made the assumption that during repose much of the linkage between the hemispheres could be effected by way of the interthalamic connections, the presence of a corpus callosum for synchronization of electroencephalographic patterns between the hemispheres thereby being made unnecessary. Opposed to this evidence is the report of Goldensohn and associates,[33] in whose case a striking absence of synchronism in electrical activity between the left and the right hemisphere, particularly in the occipital region, was observed. In all 3 cases the greatest dysrhythmia was observed between the occipital lobes. In 2·of these cases this occurred with the patient's eyes open. The obvious conclusion from the evidence so far submitted is that there is no characteristic electroencephalographic pattern by which a diagnosis of agenesis of the corpus callosum can be made. When the evidence from such tracings in many other cases has been summarized, further interesting knowledge concerning the function of the corpus callosum should be available.

SUMMARY

1. A case of agenesis of the corpus callosum diagnosed by encephalographic means during the life of a patient is reported. It is the fifteenth such case to be reported in the English literature. The presence of associated porencephaly is suggested in this case.

2. The pneumoencephalograms show dilated lateral and third ventricles, with a "bat wing" appearance in the posteroanterior view. The location of the third ventricle was higher than normal, and the foramens of Monro were widely dilated and elongated.

3. The electroencephalographic pattern in this case is definitely abnormal but cannot be considered as diagnostic of agenesis of the corpus callosum. It is characterized by irregular slow waves, absence of normal alpha activity and continuous diffuse dysrhythmia.

32. Derbyshire, A. J., and Evans, W.: A Case of Agenesis of the Corpus Callosum: Encephalographic Studies, Harper Hosp. Bull. **1**:17, 1941.

33. Goldensohn, L. N.; Clardy, E. R., and Levine, K.: Agenesis of the Corpus Callosum: Report of a Case with Neuropsychiatric, Psychologic, Electroencephalographic and Pneumoencephalographic Studies, J. Nerv. & Ment. Dis. **93**:567, 1941.

PROTECTIVE BARRIERS OF THE CENTRAL NERVOUS SYSTEM

AN EXPERIMENTAL STUDY WITH TRYPAN RED

ROBERT B. AIRD, M.D.

AND

LOUIS STRAIT, PH.D.

SAN FRANCISCO

Knowledge of the normal physiology of the blood-brain barrier and of its alteration in diseases of the central nervous system constitutes one of the interesting advances in the field of neurology in recent years. Numerous studies on infectious, toxic, degenerative and post-traumatic diseases of the central nervous system indicate that the permeability of the blood-brain and the blood–cerebrospinal fluid barrier is more or less uniformly increased in these conditions.[1] The blood-cerebrospinal fluid barrier has been shown to be impaired after such procedures as the pneumoencephalographic test, lumbar puncture, induction of spinal anesthesia, intrathecal therapeutic injection and ventriculographic examination.[1] Technics involving such procedures have even been advocated to increase the efficacy

1. Katzenelbogen, S.: The Cerebrospinal Fluid and Its Relation to the Blood: A Physiological and Clinical Study, Baltimore, Johns Hopkins Press, 1935.

This review by Katzenelbogen is good, but by no means complete. Additional references of value with respect to the alteration of the permeability of the blood-brain barrier as a result of infectious processes are: MacCurdy, J. T., and Evans, H. M.: Experimentelle Läsionen des Centralnervensystems, untersucht mit Hilfe der vitalen Färbung, Berl. klin. Wchnschr. 49:1695, 1912. McClellan, R. H., and Goodpasture, E. W.: A Method of Demonstrating Experimental Gross Lesions of Central Nervous System, J. M. Research 44:201-206, 1923. Faber, H. K.: Visualization of Preparalytic Lesions of Poliomyelitis by Intravital Staining, Proc. Soc. Exper. Biol. & Med. 35:10-12, 1936; The Early Lesions of Poliomyelitis After Intranasal Inoculation with Comments on Their Relationship to the Early Clinical Manifestations and to the Nonparalytic Cases, J. Pediat. 13:10-37, 1938.

With respect to similar changes associated with post-traumatic conditions, the following references should be included: Barbour, H. G., and Abel, J. J.: Tetanic Convulsions in Frogs Produced by Acid Fuchsin and Their Relation to the Problem of Inhibition in the Central Nervous System, J. Pharmacol. & Exper. Therap. 2:167-199, 1910. Abel, J. J.: On the Action of Drugs and the Function of the Anterior Lymph Hearts in Cardiectomized Frogs, ibid. 3:581-608, 1912. McCurdy, J. T., and Evans, H. M.: Experimentelle Läsionen des Centralnervensystems, untersucht mit Hilfe der vitalen Färbung, Berl. klin. Wchnschr. 49:1695, 1912. Sauerbruch, F.: Experimentelle Studien über die Entstehung der Epilepsie, Verhandl. d. deutsch. Gesellsch. f. Chir. 42:144-149, 1913. Macklin, C. C., and Macklin, M. T.: A Study of Brain Repair in the Rat by the Use of Trypan Blue, with Special Reference to the Vital Staining of the Macrophages, Arch. Neurol. & Psychiat. 3:353-394 (April) 1920. Dandy, W. E., and Elman, R.: Studies in Experimental Epilepsy, Bull. Johns Hopkins Hosp. 36:40-49, 1925. Morgenstern, S., and Birjukov, M.: Weitere experimentelle Ergebnisse zur Frage der Permeabilität der Gehirncapillaren, Ztschr. f. d. ges. Neurol. u. Psychiat. 113:640-650, 1928. Sawyer, W. A., and Lloyd, W.: The Use of Mice in Tests of Immunity Against Yellow Fever, J. Exper. Med. 54:533-555, 1931. Lennette, E. H., and Hudson, N. P.: Blood-Central Nervous System Barrier in Experimental Poliomyelitis, Proc. Soc. Exper. Biol. & Med. 34:470-472, 1936. Burnet, F. M., and Lush, D.: Infection of the Central Nervous System by Louping Ill Virus, Australian J. Exper. Biol. & M. Sc. 16:233-240, 1938. Browman, T.: Ueber die Farbindikatormethode als tierexperimentelle Funktionsprobe des Bluthirnschrankensystems, Skandinav. Arch. f. Physiol. 80:59-79, 1938.

of therapeutic agents which otherwise do not reach the central nervous system in effective concentrations.[1] For the most part, these studies have involved measurements of the permeability of the blood–cerebrospinal fluid barrier, and the question has been raised whether such determinations have any bearing on possible concomitant alterations in the permeability[2] of the blood-brain barrier. Since knowledge in this respect is inadequate and evidence[3] has been adduced which suggests that the blood–cerebrospinal fluid barrier and the blood-brain barrier are not comparable, but may be quite different in their permeability characteristics, the value of many of the older studies in this field has been questioned.

Although the importance of an impaired barrier in diseases of the central nervous system of toxic origin is unquestioned, the significance of similar changes occurring in infectious and post-traumatic conditions of the central nervous system remains unknown. Correspondingly, the possible therapeutic value of mechanisms which might maintain or lower the permeablity of the blood-brain barrier can only be conjectured. Such therapy for toxic conditions of the central nervous system would presumably be of major importance. For post-traumatic and infectious diseases of the central nervous system such therapy also might conceivably be of value. Knowledge of these therapeutic possibilities, however, is negligible. Aside from the possible effect of roentgen therapy[4] and the supravital dye brilliant vital red,[5] no method of lowering the permeability of the blood-brain barrier or of preventing its impairment in disease appears to be known.

The studies on brilliant vital red, carried out both on experimental animals and on patients in convulsive states, showed that the effect of the dye in lowering the permeability of the blood-brain barrier was associated with its protective action.[5] The evidence rested chiefly on the fact that in cases of experimental epilepsy brilliant vital red afforded protection against various epileptogenous agents and that direct spectrophotometric determinations showed that it lowered the permeability of the blood–cerebrospinal fluid barrier to cocaine hydrochloride. Since it was proved that the supravital dye had no central effect on the central nervous system and no peripheral effect in neutralizing or bonding with the convulsive agents, it was postulated that the action of the dye on the blood-brain barrier was similar to its measured effect on the blood–cerebrospinal fluid barrier. The fact that brilliant vital red is an acid dye and stains intensely the endothelium of both the blood–cerebrospinal fluid and the blood-brain barrier further contributed to this conclusion. Direct proof for this thesis, however, was lacking.

With these points in mind, the following studies were made in the hope of clarifying the relation between the blood–cerebrospinal fluid and the blood-brain barrier and of gaining further knowledge of the mechanisms of possible therapeutic value in lowering the permeability of these barriers.

PRELIMINARY STUDIES

In a trial of various representative supravital dyes, including brilliant vital red, congo red, trypan blue, methylene blue (methylthionine chloride) and eosin, brilliant vital red, and possibly congo red, were found to protect against the

---

2. Permeability is a much abused term. As used here in its broad sense, it refers to the selective transfer of metabolites in solution across a tissue membrane.

3. Friedemann, U.: Blood-Brain Barrier, Physiol. Rev. **22**:125-145, 1942.

4. Spiegel, E. A., and Quastler, H.: Experimentelle und klinische Untersuchungen über dem Einfluss von Röntgenstrahlen und Diathermie auf die Durchlässigkeit der Blut- Liquor-Schranke, Wien. med. Wchnschr. **31**:1059-1061, 1931.

5. Aird, R. B.: Mode of Action of Brilliant Vital Red in Epilepsy, Arch. Neurol. & Psychiat. **42**:700-723 (Oct.) 1939.

convulsive effects of strychnine sulfate, picrotoxin and cocaine hydrochloride. In another study trypan red gave striking protection against the convulsive effects of cocaine hydrochloride. The susceptibility of white mice to convulsions induced by cocaine hydrochloride was determined on a statistical basis by methods similar to those used in previous studies.[6] The criteria of convulsive involvement were the same, and susceptibility was recorded as the most severe stage attained by each mouse within a period of observation of two hours. In a second series of

TABLE 1.—*Protective Effect of Trypan Red in Experimental Epilepsy Induced in White Mice* *

Number of Injections †	Number of Mice Tested	Convulsive Effects			Convulsions and Death	Convulsive Involvement, Percentage
		None	Petit Mal	Grand Mal		
0	233	67	46	58	62	71
1	32	17	5	9	1	47
2	31	21	5	3	2	32
3	29	24	1	4	0	17
4	82	72	6	3	1	12
5	40	34	4	2	0	15
3 or more	151	130	11	9	1	14

* Induced by injection of 96 mg. of cocaine hydrochloride per kilogram of body weight.
† Each injection consisted of 0.1 cc. of a 1 per cent solution of trypan red, given intraperitoneally on separate days. The cocaine test was performed the second day after the final injection of trypan red.
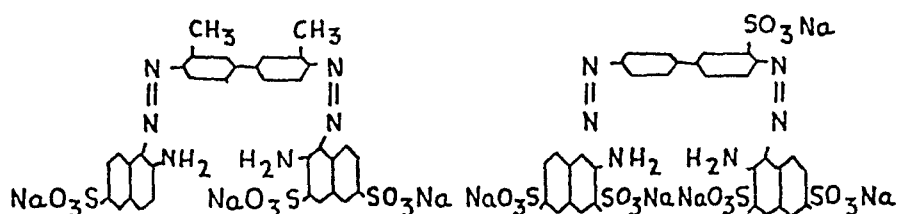
Fig. 1.—Structural formulas for brilliant vital red (C. I. no. 456), at left, and for trypan red (C. I. no. 438), at right.

experiments, white mice were given, on successive days, intraperitoneal injections of 0.1 cc. of a 1 per cent solution of trypan red (table 1), which resulted in various intensities of staining, as observed in the skin and scleras. These mice were tested with cocaine hydrochloride two days after the final injection of the dye, the dose of cocaine and conditions other than the staining being identical with those of the control group. Three or more injections of trypan red gave excellent protection over the two hour test period.

REVIEW OF LITERATURE AND HISTOLOGIC STUDIES
ON TRYPAN RED

Trypan red, the pentasodium salt of o-benzidine monosulfonic acid bisazodi-2-napthylamine-3, 6-disulfonic acid, is an acid dye of the diazo series. Structurally and chemically it is closely related to brilliant vital red (fig. 1).

Trypan red has long been used as a supravital dye.[7] It is also of interest that Ehrlich and Shiga [8] introduced its use as a therapeutic agent for trypanosomiasis.

6. (*a*) Aird, R. B., and Gurchot, C.: Protective Effect of Cholesterol in Experimental Epilepsy, Arch. Neurol. & Psychiat. **42**:491-506 (Sept.) 1939. (*b*) Aird.[5]

7. Conn, H. J.: Biological Stains, Geneva, N. Y., Biotech Publications, 1940.

8. Ehrlich, P., and Shiga, K.: Farbentherapeutische Versuche bei Trypanosomenerkrankung. Berl. klin. Wchnschr. **41**:329-332 and 362-365, 1904.

Various toxicologic investigations have been carried out on trypan red. It has been shown that this dye acts on the hematopoietic activities of the reticuloendothelial system.[9] Repeated injections in white rats produced anemia, a percentile rise in the reticulocytes, marked neutrophilic leukocytosis, granuloblastic hyperplasia and the formation of macrophages in proportion to the destruction of erythrocytes in the spleen and bone marrow. Single intraperitoneal injections of 1 cc. of a 1 per cent solution, however, produced little or no change. The lethal dose by intravenous administration in dogs was shown by Risi[10] to be approximately 80 mg. per kilogram of body weight. Lewis[11] found that slow intravenous injection of 100 cc. of a 0.25 per cent solution of trypan red in rabbits gave no ill effects, either early or late. Intravenous injections of less than 25 mg. per kilogram of body weight appear to be well tolerated. Because of the slow elimination of the dye from the tissues, an intense stain is achieved with relatively few injections and may be maintained with one injection per month, or even fewer.

Histologic studies[12] indicated that dyes of the benzidine group stain deeply, and with a fairly high degree of selective specificity, certain cells of the body: the connective tissue clasmatocytes, the macrophages of serous cavities and the endothelial cells. That these cells react intensely to the dye was indicated by the storage in their cytoplasm of large and brilliant "dye granules." The blood cells, the epithelium, the central nervous system, except for the vascular elements (choroid plexus and intracerebral blood vessels), and the meninges, however, showed no evidence of the dye.

Gross and histologic studies on mice and cats stained with trypan red amply confirmed these observations. While typical intracellular deposits appeared in the endothelial cells of the choroid plexus and brain, the ependyma, the cerebrospinal fluid and the cortical tissues failed to show any trace of the dye. In general, the results closely paralleled those obtained by staining with [brilliant] vital red.[5]

SPECTROCHEMICAL STUDIES

A more accurate evaluation of the effect of trypan red on the permeability of the blood-brain and blood–cerebrospinal fluid barriers seemed desirable. This proved feasible with the use of a spectrochemical technic which my associates and I[13] recently devised for following the distribution of cocaine throughout the body.

METHODS

Cats were used as experimental animals, inasmuch as mammals fairly high in the phylogenetic series and of moderate size (from 2 to 4 Kg. in weight) are desirable for such a study. Cocaine hydrochloride was selected as the convulsive agent because of its effect on

9. Latta, J. S., and Moore, F. H.: The Interpretation of Changes Resulting in Anemia Induced by the Intravital Dye, Trypan Red: Experimental Evidence Supporting the Monophyletic Theory of Blood Cell Origin, Folia haemat. **48**:178-209, 1932.

10. Risi, A.: Sulla chemioterapia della sostanze coloranti: Ricerche tossicologiche sul trypanrot—trypanblau e wasserblau, Rassegna di terap. e pat. clin. **5**:491-546, 1933.

11. Lewis, P. A.: The Distribution of Trypan Red to the Tissues and Vessels of the Eye as Influenced by Congestion and Early Inflammation, J. Exper. Med. **23**:669-676, 1916.

12. Evans, H. M., and Schulemann, W.: The Action of Vital Stains Belonging to the Benzidine Group, Science **39**:443-454, 1914. Evans, H. M.: The Physiology of Endothelium, Anat. Rec. **8**:99-101, 1914.

13. Strait, L.; Aird, R. B., and Weiss, S.: A Method for the Rapid Isolation and Spectrographic Measurement of Cocaine from Brain Tissue, J. Pharmacol. & Exper. Therap. **73**:363-374, 1941.

the higher cortical centers [14] and its characteristic spectral absorption,[15] which permits the detection and measurement of minute amounts with accuracy.

Narcosis was essential, as the experiments required that somewhat complicated procedures be carried out accurately on a set time schedule. Five cats were anesthetized by the intraperitoneal injection of 20 mg. of chloralose (a compound of chloral hydrate and dextrose) per kilogram of body weight, followed after forty-five minutes by 0.2 cc. of paraldehyde per kilogram. The narcosis induced varied from light to moderately deep anesthesia, the average effect in the group being adequate but not deep. Chloralose and paraldehyde were used because of their antagonistic effects on the convulsive threshold, so that when administered in combination in the doses mentioned they produce little or no alteration of the convulsive threshold, as determined by electrical stimulation.

The experimental basis for this phase of the study was established by determination of the convulsive threshold of cats to electrical stimulation under various conditions, as shown in table 2. An alternating current of 60 cycles, controlled by rheostat and variac transformer, was used as the stimulus and was measured by a highly damped thermocouple milliammeter. The duration of stimulation was one second. Needle electrodes, placed with antiseptic technic, were used to avoid difficulties which might arise from great variations in cutaneous resistance. One needle was placed across the midline of the scalp over the region of the motor cortex, and the second, in the anterior portion of the neck.

TABLE 2.—*Convulsive Threshold to Electrical Stimulation of Cats Under the Influence of Various Anesthetics and Without Anesthesia*

Anesthetic	Dose per Kg.	Narcotic Effect	Number of Cats	Number of Tests	Range of Convulsive Thresholds, Ma.	Average Convulsive Threshold, Ma.
Ether................................	....	Light	7	7	70-100	84
*Pentobarbital...................	26 mg.	Light	4	4	41- 61	52
*Paraldehyde....................	1 cc.	Moderate to deep	12	25	32-116	57
	0.2 cc.	Light	3	3	32- 49	41
*Chloralose.......	80 mg.	Deep	4	4	3- 37	14
	20 mg.	Light	3	3	13- 14	13
*Paraldehyde..................... and	0.2 cc.	Moderate	12	46	26- 77	40
Chloralose.....................	20 mg.					
No anesthetic....................	....	....	5	8	24- 66	40

* Injected intraperitoneally.

Additional studies were made to determine the effect on susceptibility to convulsions of the combined chloralose and paraldehyde anesthesia. Experimental epilepsy was induced in white mice by the use of cocaine hydrochloride under the same conditions as those observed in the previous studies of this type. One hour before injection of the cocaine hydrochloride, a test group of cats were given, by intraperitoneal injection, 20 mg. of chloralose per kilogram of weight; forty minutes later 0.2 cc. of paraldehyde was administered to the same animals by intraperitoneal injection. The results obtained in this group were then compared with those observed in previous control groups of animals to which no anesthetic had been given. The results, shown in table 3, indicated that in spite of a light anesthetic effect on the test group, there was no appreciable variation of the convulsive threshold in the two groups as determined by this technic. Since anesthesia as used in this study produced no significant alteration of the convulsive threshold either to electrical stimulation or to drugs and since all the experiments were done under identical conditions in this respect, it was assumed that the results obtained were not influenced by this phase of the procedure.

Twenty minutes after the injection of the paraldehyde, the administration of the epileptogenous agent was started. Twenty milligrams per kilogram of body weight of a 6 per cent solution of cocaine hydrochloride was injected continuously and evenly over a period of fifteen minutes by way of the left femoral vein. Although such a dose of cocaine hydro-

14. Feinberg, I.: Weitere Mittheilungen zur physiologischen Cocainwirkung, Berl. klin. Wchnschr. 24:166-168, 1887. Morita, S.: Untersuchungen an grosshirnlosen Kaninchen: II. Die Wirkung verschiedener Krampfgifte, Arch. f. exper. Path u. Pharmakol. 78:208-217, 1915.

15. Castille, A.: Ultra-Violet Absorption Spectra of the Alkaloids of the Tropeine Group, Bull. Acad. roy. de méd. de Belgique 5:193-200, 1925.

chloride is well within the ordinary convulsive range of this drug, even mild convulsive effects were observed but rarely with the slow rate of injection used. The slow injection allowed time for the cocaine to become distributed throughout the body, with a minimal loss by way of the kidney. After completion of the injection of the convulsive agent, specimens of the cerebrospinal fluid, the motor cortex and the blood were obtained at intervals of five minutes.

From 2 to 3 cc. of cerebrospinal fluid was obtained from each cat by cisternal puncture, care being taken to avoid bloody taps or contamination of the specimen by blood. This fluid was collected in a large pyrex tube and immediately frozen by insertion of the tube into carbon dioxide snow.

TABLE 3.—*Susceptibility of White Mice to Convulsions Induced with Cocaine Hydrochloride* * *Under Control and Anesthetic Conditions*

	Number of Mice	Effects				Convulsive Involvement, Percentage
		No Convulsions	Petit Mal	Grand Mal	Fits and Death	
Control group (no treatment)....	86	20	14	18	34	77
Group under anesthesia †.........	60	7	20	27	6	88

* 96 mg. per kilogram of body weight injected subcutaneously.
† Anesthesia induced by intraperitoneal injection of 20 mg. of chloralose (compound of chloral hydrate and dextrose) per kilogram of body weight (one hour before injection of cocaine) and 0.2 cc. of paraldehyde per kilogram (twenty minutes before injection of cocaine).
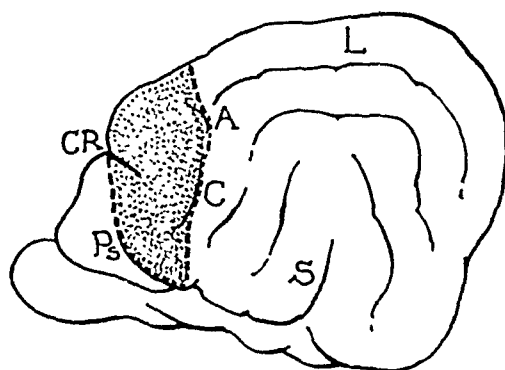
Fig. 2.—Left cerebral hemisphere of Felis domestica, showing the motor cortex and the surface lines of excision.

CR indicates sulcus cruciatus; *A*, sulcus ansatus; *L*, lateral sulcus; *C*, sulcus coronalis; *Ps*, sulcus presylvius, and *S*, sulcus pseudosylvius.

Specimens of the motor cortex, weighing from 2 to 3 Gm., were obtained from the cerebral hemisphere of each cat. The portion of cerebral cortex obtained is shown in figure 2. This consisted of the gray matter of the lateral convexity of the cerebral cortex, bordering on the sulcus cruciatus and bounded posteriorly by the sulcus ansatus and sulcus coronalis and anteriorly and inferiorly by the sulcus presylvius.[16] The dissection was carried into the white matter but avoided inclusion of the caudate nucleus. The specimens were briefly washed with water and quickly dried on clean paper towels, care being taken to eliminate all blood on the surface. Immediately after being weighed, the specimens were immersed in liquid air.

Five cubic centimeters of blood was drawn by direct cardiac puncture, injected into a large pyrex tube and immediately frozen by insertoin of the tube into carbon dioxide snow.

Although artificial respiration was occasionally required toward the end of the period during which the specimens were obtained, all samples were taken while the heart was still active and the circulation adequate. The specimens from each of the 5 cats were mixed so that, finally, for each experiment they consisted of (1) from 10 to 15 Gm. of cerebrospinal fluid, (2) from 10 to 13 Gm. of motor cortex and (3) approximately 27 Gm. of blood.

16. Brodmann, K.: Vergleichende Lokalisationslehre der Grosshirnrinde in ihren Prinzipien dargestellt auf Grund des Zellenbaues, Leipzig, Johann Ambrosius Barth, 1909. Ariëns Kappers, C. U.; Huber, G. C., and Crosby, E. C.: The Comparative Anatomy of the Nervous System of Vertebrates, Including Man, New York, The Macmillan Company, 1936.

To determine the permeability of the blood-brain barrier to epileptogenous agents, such as cocaine, used experimentally, it became necessary to refine the technic of their extraction from the brain and to increase the accuracy of their measurement considerably beyond the point permitted by older methods. With spectrochemical methods a modified technic was developed which permitted the quantitative extraction and determination in vivo of as little as 0.1 mg. of cocaine from 12 Gm. of brain, with 95 per cent recovery and an estimated error of less than 10 per cent.[13] The spectrophotometric technic possesses the added advantage that spurious results may be ruled out, the cocaine being clearly distinguishable from undesirable contaminants which follow the process of extraction and which have limited the sensitivity and accuracy of other methods.

Determinations of the concentration of cocaine in the blood were obtained in order to rule out effects other than an alteration of permeability, such as hydrolysis of cocaine in the liver or alteration of permeability in other organs or tissues, with resulting loss of the cocaine, which conceivably might be regarded as an explanation of the results observed. On the assumption that cocaine is hydrolyzed in the central nervous system, one might explain the observed results in terms of an alteration in the rate of its hydrolysis. This would not appear to be a satisfactory explanation, however, in view of the relative stability of cocaine in the organism, the large alteration in the concentration of cocaine that was found (approximately one third of the total) and the brief period of experimentation in which such a change might have occurred. That such an agent as trypan red, which does not gain entrance to the central nervous system, could cause such an alteration in the hydrolysis of cocaine in the central nervous system appears further to render this explanation untenable.

RESULTS

From the standpoint of both animal and spectrochemical technics, satisfactory [17] results were obtained on the motor cortex, the cerebrospinal fluid and the blood in all 5 of the experiments in which trypan red was used. Of 12 control experiments, satisfactory results were obtained for the motor cortex in 9, for the blood in 5 and for the cerebrospinal fluid in 7. The original data obtained from these experiments and the summary are presented in tables 4 and 5.

TABLE 4.—*Spectrochemical Determination of the Distribution of Cocaine Hydrochloride With and Without Treatment With Trypan Red*

Treatment	Experiment No.	Motor Cortex *	Blood *	Cerebrospinal Fluid *
None..........................	1	84.5	†	†
	2	†	†	6.25
	3	56.9	13.8	10.85
	4	73.8	20.4	8.55
	5	84.0	†	8.9
	6	62.5	16.7	8.55
	7	60.4	†	8.15
	8	66.1	†	†
	9	52.8	13.6	8.65
	10	53.7	20.6	†
Four intraperitoneal injections of 5 cc. of 1% trypan red	1	46.3	14.4	6.12
	2	31.4	10.9	4.45
	3	43.6	14.0	5.14
	4	33.6	13.7	4.72
	5	32.7	14.7	4.96

* Milligrams of cocaine hydrochloride per gram of tissue × 1,000.
† The majority of these samples either were lost in the process of extraction or were discarded before measurement because of unsatisfactory absorption spectrums.

The statistical mean concentration of cocaine in the motor cortex of the cats which were not treated with trypan red was 0.066 ± 0.003 mg. per gram. The concentration in the motor cortex of the treated animals was notably lower, 0.038 ± 0.002 mg. per gram. The odds are about 375,000,000 to 1 that this alteration in value may be due to chance. In contrast to concentrations in the brain, those in the blood for both treated and untreated animals differed but

17. "Satisfactory" refers merely to the samples which were not lost in the course of the extraction or which were not discarded before measurement because they did not satisfy objective criteria for photometric determination.

slightly. The mean concentrations in the blood for untreated and treated animals were respectively 0.017 ± 0.001 and 0.014 ± 0.0005 mg. per gram. The odds of 24 to 1 that this difference was due to chance may be dismissed by statistical criteria. It is conceivable, however, that this slight difference, although of no importance to the conclusions reached here, may be real and indicative of a slight increase in renal excretion, due to a toxicity for the kidneys of the trypan red in the concentrations used in these experiments. The concentrations in the cerebrospinal fluid for the treated and the untreated animals were lower than the concentrations in the blood and brain; [18] they were respectively 0.0086 ± 0.00008 and 0.0051 ± 0.0002 mg per gram. As in the case of the motor cortex, the difference in concentration between the treated and the untreated group is great, and the odds against a chance result, 10^{23} to 1, are impressive.

A schematic representation of the data showing the relative distribution of cocaine and the alterations in the mean concentrations of cocaine in these experiments is given in figure 3. That the concentrations in the various tissues of the same animals lie within sharply defined boundary lines attests to the reliability

TABLE 5.—*Summary of Results and Statistical Analysis of Alteration of Permeability of Blood-Brain and Blood–Cerebrospinal Fluid Barriers to Cocaine Hydrochloride* After Treatment with Trypan Red*

Specimen	Treatment	Number of Experiments	Total Number of Cats	Arithmetical Mean, M (Mg./Gm. × 1,000)	Standard Deviation, σ	Standard Deviation of Difference, D	Significance Test t's — t's D	Odds †
Motor cortex	Treated ‡..........	5	25	37.52 (Mₜ)	2.8	4.95	5.77	3.75 — 10⁸
	Untreated (control)	9	45	66.1 (Mᵤ)	4.08			
Blood	Treated ‡..........	5	25	13.51 (Mₜ)	0.682	1.67	2.08	24
	Untreated (control)	5	25	17.02 (Mᵤ)	1.52			
Cerebrospinal fluid	Treated ‡..........	5	25	5.08 (Mₜ)	0.285	0.31	11.24	Approximately 1 × 10²³
	Untreated (control)	7	35	8.56 (Mᵤ)	0.121			

* 20 mg. per kilogram of body weight injected intravenously.
† Odds against the results being due to chance.
‡ Four daily intraperitoneal injections of 5 cc. of a 1 per cent solution of trypan red.

of the experimental results. Diagrammatically, this area is the equivalent of a uniform coefficient of variation of the mean values of concentration for each tissue and indicates a high degree of internal consistency for the data.

These results clearly indicate that in the presence of concentrations of cocaine in the blood which were essentially the same in groups of cats given trypan red and those not given the dye, significant alterations in the passage of cocaine through the blood-brain and the blood–cerebrospinal fluid barrier occurred after supravital staining with trypan red. The amount of cocaine reaching the motor cortex was reduced by approximately 31 per cent and that reaching the cerebrospinal fluid by 40 per cent in the cats treated with the dye as compared with similar groups of animals not so treated.

COMMENT

The parallelism between the related supravital dyes trypan red and brilliant vital red appears to be close. Both dyes stain intensely the endothelial components

18. The distribution of cocaine in the tissues and the possible significance of such data with respect to the pharmacodynamic action of cocaine will be given elsewhere.

of the blood-brain and the blood–cerebrospinal fluid barrier but do not stain the ependyma, the nerve tissue proper or the cerebrospinal fluid. Like brilliant vital red, trypan red protects in experimental convulsive states. In dogs the passage of cocaine across the blood–cerebrospinal fluid barrier was reduced approximately 40 per cent after they were stained with brilliant vital red.[5] Correspondingly, after cats were stained with trypan red, the amounts of cocaine which passed the blood-brain and the blood–cerebrospinal fluid barrier were lowered 31 and 40 per cent respectively. By analogy, then, the present results appear further to corroborate the conclusion reached in the study of brilliant vital red,[5] namely, that the dye significantly altered (lowered) the permeability of the blood-brain barrier.

Considerable evidence has been adduced with respect to the permeabilities of the blood-brain and the blood–cerebrospinal fluid barrier for dyes, drugs, toxins,
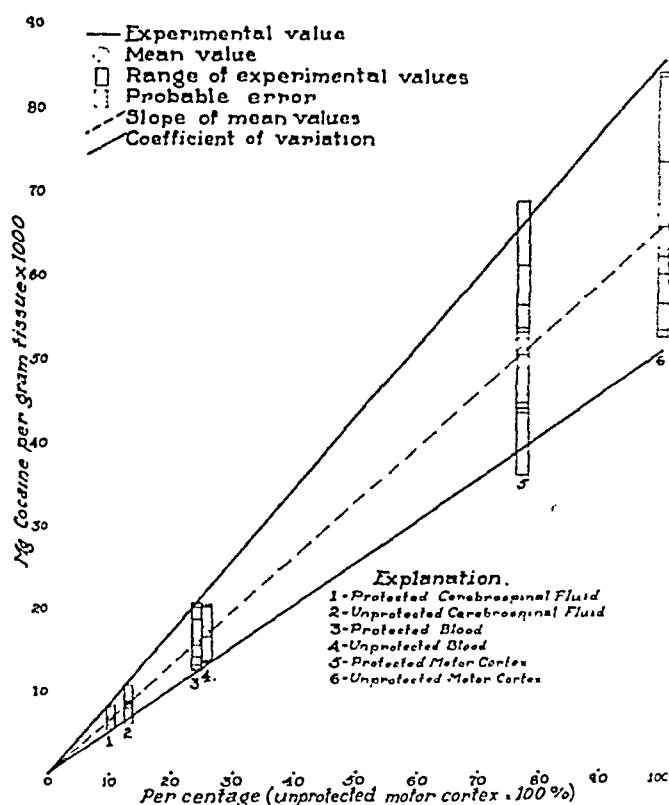
Fig. 3.—Spot graph of spectrophotometric determinations on groups of cats, treated with trypan red and without such treatment, showing the relative distribution of cocaine in the motor cortex and the cerebrospinal fluid, the range of variations in the determinations, the arithmetical means and probable errors of the determinations and the percentage of difference between the average amount of cocaine found in the tissues of animals treated with trypan red and the average amount in tissues of the animals which were not treated.

antibodies and viruses.[3] These studies have been interpreted as showing that these two barriers differ widely in their permeabilities, depending on the electrical charge of the permeating substance. Certain unexplained exceptions, however, have been noted. In this connection, it is of interest that in the present experiments the alkaloid cocaine, which presumably possesses the same electrical charge (probably positively charged in the basic blood stream) for both barriers, was found to pass both barriers. Furthermore, both barriers were modified in these experiments in the same direction, and roughly to the same degree, by the action of trypan red.

The fact that more cocaine was found in the brain than in the cerebrospinal fluid might be interpreted as indicating a difference in the permeability of the two barriers. The higher concentration of cocaine in the brain, however, may merely reflect the greater relative solubility of cocaine in the lipids of the brain than in the aqueously constituted cerebrospinal fluid or the blood, with its colloidal character.

The alterations in permeability of the blood-brain and the blood–cerebrospinal fluid barrier observed in this study, therefore, verify the hypothesis of Spatz [19] that the endothelium is the locus of the barrier between the blood and the central nervous system. Although these results contradict the beliefs expressed by Krogh [20] and Ehrlich,[21] who denied the existence of any selective capillary permeability, they are entirely in accordance with the position held by King.[22] King expressed the opinion that the permeabilities of the blood-brain and the blood–cerebrospinal fluid barrier are not necessarily different and explained the apparent difference in terms of the "affinity" of the brain in the case of the blood-brain barrier and its corresponding absence in the case of the blood–cerebrospinal fluid barrier.

Used in a broad sense, permeability refers to the selective transfer of metabolites in solution from the medium on one side of a tissue membrane to the medium on the other side. As indicated by the laws governing the Donnan equilibrium, and as recently shown by the interesting studies of Younge and Hurst,[23] the constitution of the mediums is an important factor and cannot be dissociated from the over-all consideration of the permeability of the membrane in its natural environment. For these reasons, even though the endothelial components of the blood-brain and the blood–cerebrospinal fluid barrier might be essentially identical, the permeabilities of these barriers are probably somewhat different. Owing to the presence of the brain and its attendant metabolic activity, the extracellular fluid of the brain is presumably considerably different from the cerebrospinal fluid, at least from the cerebrospinal fluid originating in the choroid plexus. The presence of the brain, then, might conceivably alter, indirectly but appreciably, the permeability of the blood-brain barrier from that obtaining in the blood–cerebrospinal fluid barrier. This alteration was inferred by King.[22]

It is important in this connection to define the term "blood-brain barrier." Although this term implies a single barrier between the blood and the brain, it is clear, as already indicated, that this appellation should be restricted to designate those structures which separate the blood from the extracellular fluid of the brain, namely, the endothelium of the capillaries supplying the brain together with their investing sheaths. The endothelium appears to be the important component of this barrier, inasmuch as the supravital dyes, brilliant vital red and trypan red, although modifying its permeability, do not gain entrance to the central nervous system in significant amounts and stain only the endothelium.

19. Spatz, H.: Die Bedeutung der vitalen Färbung für die Lehre vom Stoffaustausch zwischen dem Zentralnervensystem und dem übrigen Körper, Arch. f. Psychiat. **101**:267-358 1934.

20. Krogh, A.: The Anatomy and Physiology of Capillaries, New Haven, Conn., Yale University Press, 1922, pp. 204-205.

21. Ehrlich, P.: Ueber die Berziehungen von chemischer Constitution, Vertheilung und pharmakologischer Wirkung, in Gesammelte Arbeiten zur Immunitätsforschung, Berlin, A. Hirschwald, 1904, p. 573.

22. King, L. S.: The Hematoencephalic Barrier, Arch. Neurol. & Psychiat. **41**:51-72 (Jan.) 1939.

23. Younge, C. M.: On the Nature and Permeability of Chitin: II. The Permeability of the Uncalcified Chitin Lining; The Foregut of Homarus, Proc. Roy. Soc., London s.B. **120**:15-41, 1936. Hurst, H.: Permeability of Insect Cuticle, Nature, London **145**:462-463, 1940; Insect Cuticle as an Asymmetrical Membrane, ibid. **147**:388-389, 1941.

It is suggested by these studies, as well as by anatomic and physiologic considerations, that the cell membranes of the cortical tissue form a second, and even more important, barrier, which may be termed the "cortical barrier." The interface between the lipoidal nerve tissue and the aqueous extracellular fluid undoubtedly possesses complex surface properties and semipermeable characteristics capable of the selective activity essential for function as a barrier. Since this barrier controls the transfer of metabolites concerned with the oxygenation and nutrition of the cells as well as the elimination of the waste products of cellular metabolism, it presumably plays a vital role in the physiology of the brain. A schematic representation of these barriers is shown in figure 4.

A considerable amount of the conflicting evidence adduced in the numerous studies which have been made on the blood-brain and the blood–cerebrospinal fluid barrier may be explained, in part at least, by the failure to consider this second, more central, barrier formed by the cell membranes of the cortical tissue. This is particularly true of those studies in which the interpretation of results depended on the effects of drugs on the cortex and which, therefore, directly
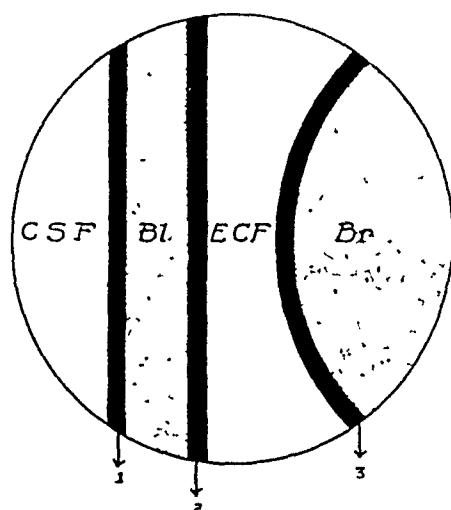
Fig. 4.—Schematic diagram of the blood-cerebrospinal fluid barrier (*1*), the blood-brain barrier (*2*) and the cortical barrier (*3*).

CSF indicates cerebrospinal fluid; *Bl*, blood; *ECF*, extracellular fluid of the brain, and *Br*, cellular constituents of the brain.

involved this cortical barrier. Much that King[22] would account for in terms of the "affinity of the nervous tissue" might be thus explained. It is not necessary to think of the cortical barrier alone as modifying the passage of drugs or of metabolites from the extracellular to the intracellular spaces. Equally important is any modification of surface properties, with a direct effect on cellular reactivity or secondary effects arising from the ability of centrally acting drugs to attach themselves to the cells. It is conceivable that the blood-brain barrier may be comparable to the blood–cerebrospinal fluid barrier but that, because of the secondary effects of the cortical barrier, experimental results on the two may appear to be very different. Such possibilities have not been properly emphasized in even the most recent review of literature concerned with the blood-brain barrier.[3]

The implications of the results of this study with respect to susceptibility to convulsions are the same as those discussed in the previous study on brilliant vital red.[5] It should be stressed, however, that, although the experimental approach used in this study depends on direct measurements of permeability and the posi-

tive results obtained may be interpreted as favoring a toxic factor in epilepsy, it should not be assumed that all forms of epilepsy are necessarily of this type. Knowledge of the various forms of the convulsive state suggests that this condition cannot be explained so simply.

The arguments in favor of a toxic form of epilepsy and the limitations of this concept need not be repeated. It is emphasized that numerous complex physiologic and biochemical changes are associated with an alteration of the semipermeable characteristics of the tissue membranes, and since these changes occur together, it is not possible to say that any single factor or combination of factors is responsible for any resulting physiologic effect. Water balance, shifts of acid-base balance and other factors affect the permeability of the tissue, and in turn are affected by such changes. Although the alteration of permeability in itself is presumably of the greatest importance in this study of epileptic convulsions induced by drugs, it is conceivable that one of the changes associated with this alteration may be the precipitating factor in human epilepsy. More likely still is the possibility that the convulsive state is a result of the whole complex of changes, that is, that the changes associated with increased permeability in cortical tissue cause a more unstable and irritable state, which, in turn, is characterized by an increased susceptibility to convulsions. As has been pointed out in previous articles,[6] those mechanisms which are known to increase the permeability of tissue, such as alkalosis, hydration, anoxemia and inflammatory changes, are also known to lower the convulsive threshold. As a single mechanism of fundamental neurophysiologic importance in determining cellular nutrition and reactivity, premeability, or rather the complex of changes associated with alterations of permeability, offers an attractive hypothesis for the numerous, and otherwise unrelated, factors known to be of importance in modifying convulsive reactivity.[6b]

A more obvious, and possibly more important, implication of this study lies in its possible therapeutic application to toxic and degenerative diseases of the central nervous system. It is conceivable that the vital dye might protect against other toxic disease of the central nervous system (retrobulbar neuritis; eclampsia; lead encephalopathy; arsenic poisoning), as well as against toxic convulsive states. In addition, various degenerative diseases of the central nervous system, which are known or assumed to have a toxic origin, such as amyotrophic lateral sclerosis, Landry's paralysis, progressive muscular atrophy and multiple sclerosis, might be benefited by such therapy. Cobb and associates[24] found that brilliant vital red protects against triphenylphosphite used as a convulsive agent. Studies by one of us (R. A.) and associates[25] indicated that triphenylphosphite is quickly hydrolyzed after its injection and that two distinct effects may be ascribed to its breakdown products. The phenol fraction produces early convulsive effects at the level of the cord, while the phosphorous acid fraction causes delayed degenerative effects in the cord and brain stem.[26] Regardless of these mechanisms of action, the fact remains that the supravital dye afforded protection against such toxic effects, both the early convulsive and the late degenerative complications. The therapeutic possibilities and importance of this discovery, therefore, appear to

24. Cobb, S.; Cohen, M. E., and Ney, J.: Brilliant Vital Red as an Anticonvulsant, J. Nerv. & Ment. Dis. **85**:438-441, 1937; Anticonvulsive Action of Vital Dyes, Arch. Neurol. & Psychiat. **40**:1156-1177 (Dec.) 1938.

25. Aird, R. B.; Cohen, W. E., and Weiss, S.: Convulsive Action of Triphenyl Phosphite, Proc. Soc. Exper. Biol. & Med. **45**:306-309, 1940.

26. Smith, M. I.; Lillie, R. D.; Elvove, E., and Stohlman, E. F.: The Pharmacological Action of the Phosphorus Acid Esters of the Phenols, J. Pharmacol. & Exper. Therap. **49**:79-99, 1933.

be considerable. The systematic clinical trial of these agents, or similar substances which may be discovered, seems to be justified. Such studies are now in progress. It is hoped that the present encouraging results will warrant a fuller and more comprehensive clinical report later.

SUMMARY AND CONCLUSIONS

Trypan red, a supravital diazo dye closely related to brilliant vital red, was found to parallel the latter in its staining properties and its physiologic effect in lowering the permeability of the blood-brain and the blood–cerebrospinal fluid barrier. The distribution of cocaine in the motor cortex, the cerebrospinal fluid and the blood of cats was accurately determined by spectrochemical methods under standard conditions. When similar groups of cats were stained with trypan red, the amount of cocaine entering the cortex was lowered by 31 per cent and that entering the cerebrospinal fluid was decreased by 40 per cent, while the concentration in the blood remained essentially the same.

The alteration in permeability of the blood-brain barrier associated with the selective staining of the endothelial elements of this barrier verifies the hypothesis of Spatz that the locus of the barrier between the blood and the extracellular fluid of the brain lies in the endothelium of the intracerebral vessels. The similar alteration in the permeability of the blood–cerebrospinal fluid barrier constitutes strong evidence in favor of the cogent arguments of King that the permeability of the endothelium of the blood–cerebrospinal fluid barrier is not necessarily different from that of the endothelium of the blood-brain barrier and emphasizes the importance of the brain in explaining apparent differences in the permeability of these two barriers. It is pointed out that the term "blood-brain barrier" is confusing and that, if the name is to be retained, it should be restricted to the barrier between the blood and the extracellular fluid of the brain. The presence of a third barrier, located in the cell membranes of the cortical tissue, is stressed.

The results obtained in this study suggest that changes in the permeabliity of the blood-brain and the cortical barrier, or factors associated with such changes, are of fundamental neurophysiologic importance in determining susceptibility to convulsions. Although these results, which depend on the induction of experimental epilepsy by convulsive drugs, might be interpreted as favoring the theory of a toxic origin of the convulsive state, it is suggested that any biochemical, neurophysiologic or neuropathologic change which modifies, either directly or indirectly, the permeability of the blood-brain barrier or the cortical tissue will have a corresponding effect on the susceptibility to convulsions.

In view of the fact that the permeability of the blood-brain barrier is increased in various diseases affecting the central nervous system, knowledge as to mechanisms which lower the permeability of this barrier may well prove to be of clinical importance. The therapeutic possibilities of such mechanisms are considerable, and their trial in treatment of toxic and degenerative conditions of the central nervous system appears to be justified.

University of California Hospital.

CEREBELLAR SYNDROME FOLLOWING HEAT STROKE

WALTER FREEMAN, M.D., Ph.D.

AND

EDITH DUMOFF, M.D.

WASHINGTON, D. C.

The lethal effects of high body temperatures are well known; nevertheless, over brief periods the temperature may rise as high as 111 F., or even higher, with rapid and complete recovery. The period must be brief because at such high temperatures the pathologic alterations in the body cells rapidly become irreversible. The cells of the central nervous system are particularly susceptible to any prolonged nocive influence, such as anoxia, trauma, alcohol and bromide intoxication; hence it is not surprising to find that fever itself induces rapid and severe alterations. In this paper we shall point out that certain cells in the central nervous system are more liable to specific pathologic changes in that borderland of heat stroke between total death and total recovery. Numerous cases of so-called neurotic sequels to heat stroke have been reported, but few in which the pathologic process was so strikingly indicated by clinical symptoms pointing to cerebellar dysfunction as in the one (case 2) to be reported.

We have had the opportunity to survey the material in the Army Medical Museum, by permission of its curator, Colonel J. E. Ash, and have selected a case (Acc. 69622) of heat stroke in which the patient survived long enough to show beginning pathologic changes in the cerebellar ganglion cells (case 1).

REPORT OF CASES

CASE 1.—A 60 year old inmate of the Soldier's Home was admitted to the hospital on July 27, 1940, during a prolonged spell of very hot weather, because of sudden unconsciousness. His axillary temperature was 109 F. Physical examination revealed pinpoint pupils, hot and dry skin and absence of deep reflexes. In spite of intensive antipyretic measures, at the end of two hours his temperature was 106 F. He remained comatose. The following morning his temperature was 102 F. He died approximately twenty hours after admission.

Necropsy.—There were edema and congestion of the lungs, hypertrophy of the heart, chronic passive congestion of the liver, fibrosis of the spleen and cholelithiasis. The brain was swollen, and the cerebrospinal fluid was decreased. The vessels of the meninges, as well as those of the cortex and the basal nuclei, were congested. Section of the brain showed several small areas of old softening. Microscopic examination revealed generalized congestion and edema. The ganglion cells of the cerebral cortex were pale and swollen, with enlarged pericellular spaces, although their nuclei were usually still visible. The presence of some old arteriosclerotic lesions was verified. The arteries of the basal ganglia showed conspicuous infiltration of their walls with iron. Several small arteries in the vicinity of the third ventricle presented fresh ring hemorrhages. Sections of the cerebellum showed congestion with marked edema, especially of the molecular layer. The Purkinje cells were severely affected, many being absent and the rest in a state of coagulation necrosis, with loss of Nissl bodies and small opaque nuclei (fig. 1). The processes could be followed only a short distance. There was no cellular infiltration or glial reaction. The cells of the dentate nucleus were much less seriously affected, and those of the granule layer seemed only moderately damaged.

Brouwer,[1] in 1913, reported a case of a man aged 30, with no previous symptoms, who died while working in an overheated bakery. There was no record of this

1. Brouwer, B.: Ueber Hemiatrophia neocerebellaris, Arch. f. Psychiat. **51**:539, 1913.

patient's temperature. Noteworthy postmortem observations were atrophy of the left cerebellar hemisphere to one-third the normal size and atrophy of the corpus dentatum, the cerebellar cortex and the pons on the opposite side. The actual lesion was confined to the cerebellar cortex, which showed pronounced atrophy to the molecular zone, the Purkinje cells being almost entirely absent and the granular layer reduced to a thin layer of rather large cells. In view of the unilateral changes, we believe this case may have been one of silent cerebellar hemiatrophy.

Schwab,[2] in 1925, reported autopsy observations on animals which had been exposed to radiating heat from the sun. There was generalized venous hyperemia,
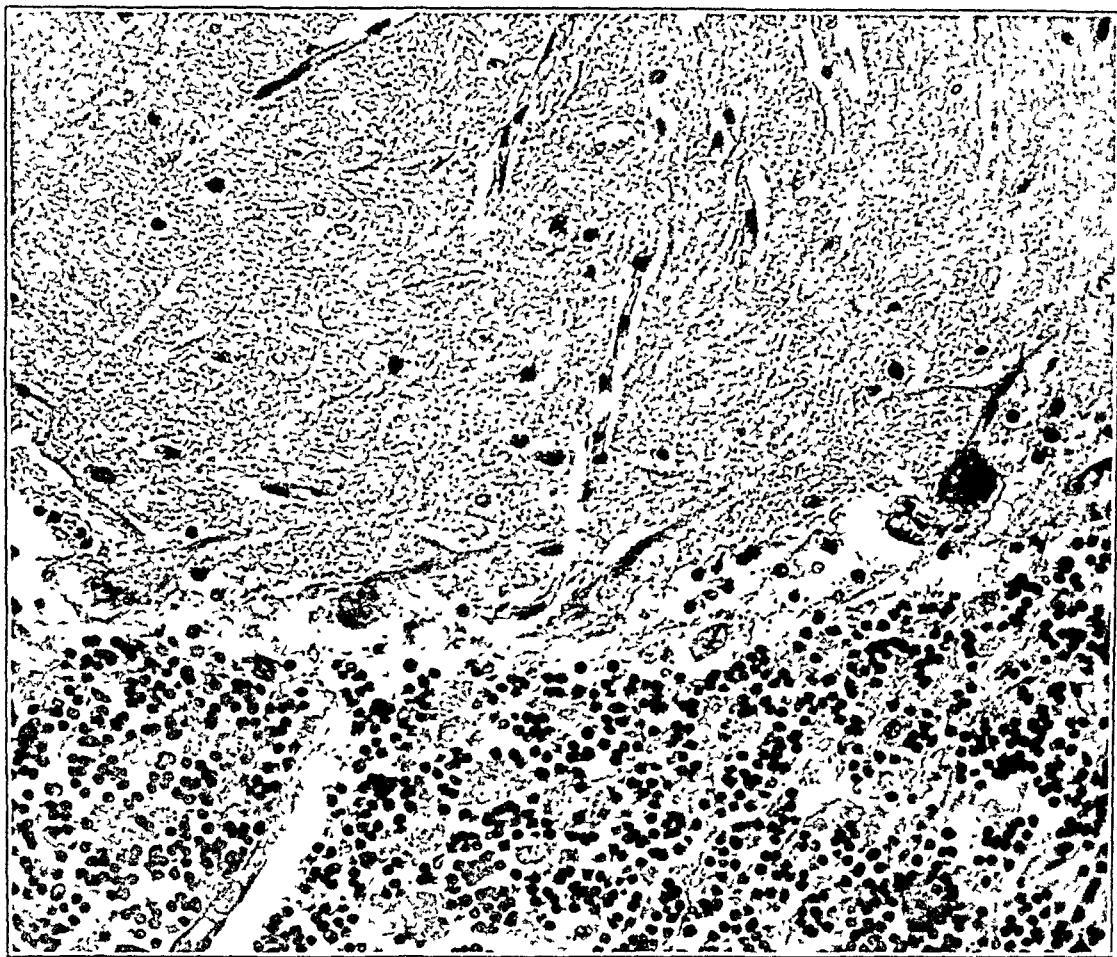
Fig. 1 (case 1).—Necrosis of remaining Purkinje cells following heat stroke (courtesy of United States Army Medical Museum, acc. no. 69622) ; × 285.

particularly notable in the meninges. The ganglion cells and Purkinje cells of the cerebellum showed disintegration of Nissl bodies, in proportion to the period of exposure. These changes were demonstrable as early as three hours after exposure, while the ventral horn cells were less intensely involved. Schwab also noted that postmortem studies on patients who died of sunstroke showed petechiae and smaller or larger ecchymoses of the serous membranes, and sometimes of the meninges and various parts of the nervous system. He also noted disintegration of Nissl bodies. In his review, he cited a case reported by A. Cramer, in 1890, in

2. Schwab, W.: Brain Changes in Sunstroke, J. A. M. A. **84:**712 (Feb. 28) 1925.

which the patient died three months after insolation, during which period severe mental disturbances were present. Autopsy revealed extensive atrophy of the cortical fibers of the cerebrum and the cerebellum alike, while the ganglion cells were intact. Schwab's own case was that of a man aged 25 who died two days after being stricken. Autopsy showed that the convolutions were flattened and the surface of the brain extremely dry. The entire medullary substance was filled with scattered petechiae, most numerous at the level of the corpus callosum. The cortical substance showed disintegration of Nissl bodies but no neuronophagia.

In 1937, Hartman [3] reported a case and the results of experimental work in this field. His patient, a white man aged 31, had been given fever therapy for bilateral iridocyclitis. The first six treatments, given at five to seven day intervals, were each of five hours' duration, and the temperature ranged from 103 to 107.4 F. After this series, treatments were discontinued for about six months and then resumed. The patient received six similar treatments, with no untoward effects. Immediately after the seventh treatment he went into shock and died twenty hours later. The height of the temperature during fever was not reported. Autopsy revealed that the right lobe of the cerebellum was a soft, hemorrhagic, necrotic mass. Sections from the cerebrum showed marked edema, with unusually large clear spaces about the smaller vessels and about many of the pyramidal cells. The pyramidal cells themselves stained poorly. The nuclei were broken up, and Nissl bodies could not be made out. Sections from the better preserved, left lobe of the cerebellum showed considerable congestion and some diffuse hemorrhage. The Purkinje cells were poorly stained and the nuclei pyknotic. Tissue of the necrotic right lobe took a homogeneous pink stain, although nuclei here and there stained poorly. There was extensive hemorrhagic infiltration. No evidence of thrombosed blood vessels could be made out.

Hartman exposed 15 animals to high temperatures for definite periods. He stated:

Constant and severe anoxia is shown by the decreased oxygen saturation of the arterial blood and the low oxygen content of the venous blood in animals after fever therapy. . . .

Factors producing anoxia during fever therapy are alkalosis, accelerated blood flow, increased temperature of the blood and increased demand for oxygen in the tissues. The last results from the increased metabolism and the depressed utilization of oxygen of the tissues, especially the brain, were due to the histotoxic effect of the sedatives used.

In 1918 Stewart [4] reported a case of cerebellar syndrome following heat stroke. A soldier aged 32 was found unconscious after marching a mile (1.6 kilometers) in the sun, the temperature being 109 F. in the shade. His temperature remained high for six days, during which time he was comatose and incontinent and all deep reflexes were absent. Ten days after the onset of illness examination revealed exaggerated tendon reflexes; severe ataxia; incoordination of movements in the arms and legs; athetoid movements when he grasped objects; scanning, indistinct speech, and pronounced nystagmus. One year later the patient was described as hyperemotional, but well oriented and with good insight. He displayed notable incoordination and ataxia of the cerebellar type, marked dysmetria of all movements, asynergia, adiadokokinesis and cerebellar catalepsy.

In 1912 Weisenburg [5] reported a case of severe sunstroke followed by multiple nervous lesions, producing mania, convulsions and coma, followed by acute

3. Hartman, F. W.: Lesions of the Brain Following Fever Therapy, J. A. M. A. **109**:2116 (Dec. 25) 1937.

4. Stewart, R. M.: Occurrence of a Cerebellar Syndrome Following Heatstroke, Rev. Neurol. & Psychiat. **16**:78, 1918.

5. Weisenburg, T. H.: Nervous Symptoms Following Sunstroke, J. A. M. A. **58**:2015 (June 29) 1912.

cerebellar ataxia, loss of speech and spastic symptoms. The temperature, initially
107 F., did not become normal until twenty-two days later. In reviewing the
literature up to this time, Weisenburg referred to 2 cases reported by Nonne, 1 in
1905 and 1 in 1907, in which acute ataxia followed overheating.

CASE 2.—A white man aged 38, with chronic alcoholism, was admitted by ambulance to the
Central Dispensary and Emergency Hospital, service of Dr. M. W. Perry and Dr. W. K. Myers,
on Aug. 8, 1937. The axillary temperature was 108 F. and the pulse rate 160, and he had
profuse watery diarrhea shortly after admission. He was immersed in ice water for twenty
minutes and then wrapped in wet sheets and exposed to an electric fan. On admission to
the ward one hour later his temperature was 100.8 F. by rectum. In the next twelve hours
he received 3,000 cc. of isotonic solution of sodium chloride intravenously. When he became
rational he gave the following story: The day before admission, while working out of doors
at a temperature of 106 F., he felt ill. That night he drank three bottles of beer. The next
day he stayed home, feeling unable to work. He took a large quantity of water but did not
perspire. His mind was completely clear until he fell to the floor, after dinner.

After emergency measures were carried out, the temperature was 101 F., the pulse rate 86,
the respiratory rate 20 and the blood pressure 140 systolic and 85 diastolic. There were
severe nystagmus on any motion or attempt at fixation, thickness of speech, intention tremor

Fig. 2 (case 2).—Encephalogram, showing cerebellar atrophy following heat stroke.

and poor coordination of movement. No motor or sensory loss was apparent. His temperature
remained elevated until August 22 (fourteen days) and then gradually fell to normal in the
next five days. He was discharged from the hospital on September 14, with his neurologic
status unchanged.

On Oct. 1, 1937 he was admitted to the psychopathic ward of Gallinger Municipal Hospital
for mental observation. At this time the examiner made the following note: "The patient
is lying in bed; he is unable to stand or to sit up in bed. He has a pronounced speech defect;
frequently his production is utterly unintelligible. He is oriented in all fields. Incoordina-
tion is present in both upper and lower extremities. Tremor is accentuated on active motion."

Examination on November 19 showed notable incoordination on heel to shin and finger
to nose tests and marked tremor, which was accentuated on movement. The deep reflexes
in the upper extremities were increased. The examiner noted motor dysarthria, due to
incoordination of the lips and tongue. The patient became stronger; his speech improved,
and he was able to raise himself up in bed and to maintain himself in a chair for several
hours. He was discharged on Nov. 22.

· On April 15, 1940 he was admitted to the neurologic service of Gallinger Municipal
Hospital, at which time examination revealed slow, aimless, purposeless movements of the
arms and legs when the patient was talking; slurred speech; spastic, slapping gait, and
complete incoordination. An encephalogram on April 17 showed a large collection of air
overlying the cerebellum (fig. 2) and a conspicuously dilated fourth ventricle, but no other
abnormality.

He was again received in the ward for patients with neurologic diseases of Gallinger Municipal Hospital, on Jan. 14, 1941. On this admission he could walk, but not without assistance, and he expressed a constant fear of falling. The neurologic status was little changed.

The patient was readmitted to Gallinger Municipal Hospital for follow-up studies on Oct. 15, 1942. At this time he added the information that in 1926 he had had a heat stroke, with vertigo, nausea and vomiting, and was bedridden for two days. At the time of the present admission his speech showed improvement. In spite of the Irish brogue and the dysarthria, it was not difficult to understand him. In the preceding year he had regained sensibility to light touch over the lower extremities. The senses of taste and smell were impaired after the stroke but had improved in the past year, so that he enjoyed smoking and could distinguish odors and flavors.

On the present admission he adjusted himself quickly to ward routine. He was able to get out of bed without assistance and, by holding on to the bed, could take the necessary step or two to reach the wheel chair, in which he spent most of his time. He had a fixed facial expression, but when he was spoken to he usually broke into an extremely broad grin, which

Fig. 3 (case 2).—Cerebellar ataxia and grimacing shown by patient in attempting to grasp a fountain pen.

Fig. 4 (case 2).—Signature of the patient.

accentuated the droop of the right corner of the mouth and the ptosis of the right lower eyelid. When he talked there were notable slapping of the tongue and incoordinate twisting of the lips, together with purposeless, slow, somewhat athetoid movements of the hands. Dysmetria, ataxia ·and adiadokokinesis were all pronounced and equal on the two sides (fig. 3). Hypotonicity was not remarkable except in the hands. No pathologic reflexes were elicited. Sensory perception was normal in all fields. He could stand unassisted for only a few seconds at a time, with the feet very wide apart and the trunk tending to lean forward from the hips. There was notable incoordination in gait, the trunk lurching first backward and then forward; the legs, flexed at the hips and remaining in extension at the knee, were lifted high and slapped forcibly to the ground. His handwriting was large and childlike, but he was proud of his ability to write his name (fig. 4). No nystagmus was noted during this admission. Psychometric examination revealed that his intelligence was superior to that of the average unskilled laborer, the intelligence quotient being 94. Memory was good; reasoning ability and judgment were unimpaired, and his ability to think in abstract terms was equal to that of the average adult.

CONCLUSION

A patient who had survived a period of extreme hyperthermia of about fourteen days presented the signs of cerebellar syndrome within forty-eight hours after the onset of illness. Cerebellar degeneration was observed post mortem in another patient who died after about twenty hours of hyperpyrexia associated with sunstroke. We believe that the most permanent and significant pathologic change in cases of cerebellar syndrome following hyperpyrexia is destruction of the Purkinje cells of the cerebellar cortex.

1028 Connecticut Avenue.
Gallinger Municipal Hospital.

CEREBRAL ARTERIOVENOUS OXYGEN DIFFERENCE

II. MENTAL DEFICIENCY

HAROLD E. HIMWICH, M.D.

AND

JOSEPH F. FAZEKAS

ALBANY, N. Y.

Previous observations on patients with mental deficiencies include studies of cerebral arteriovenous oxygen differences associated with mongolism,[1] cretinism,[2] phenylpyruvic oligophrenia [1] and undifferentiated mental deficiency.[3] The purpose of the present communication is to extend these observations to patients with amaurotic familial idiocy, hydrocephalus and microcephaly. The combined data present the opportunity for comparison of the cerebral arteriovenous oxygen differences associated with the various types of mental deficiency. The methods for the collection and analysis of the cerebral arterial and venous blood are the same as those described in part I of this series.[3]

RESULTS

Amaurotic Familial Idiocy.—Eleven observations on the cerebral arteriovenous oxygen differences for the 3 patients with amaurotic familial idiocy, between 1 to 1½ years of age, are presented in table 1. The average for 6 observations in which

TABLE 1.—*Cerebral Arteriovenous Oxygen Differences in Patients with Amaurotic Familial Idiocy for Cerebral Blood from Internal Jugular Vein and from the Fontanel*

Internal Jugular Vein, Vol. per Cent	Fontanel, Vol. per Cent
6.4	7.3
5.7	7.4
6.2	7.7
5.8	6.6
4.3	8.6
5.8	
Average 5.7	7.5

the arterial blood was compared with the internal jugular venous blood was 5.7 volumes per cent, and the average for 5 observations made by comparison of arterial blood with blood from the fontanel was 7.5 volumes per cent. The values for the cerebral arteriovenous oxygen differences for the children with amaurotic familial idiocy were closer to those for the newborn (8.6 volumes per cent [3]) than they were to children of their own age. The values obtained for the children with amaurotic familial idiocy may be compared with the average value of 3.4 volumes

1. Himwich, H. E., and Fazekas, J. F.: Cerebral Metabolism in Mongolian Idiocy and Phenylpyruvic Oligophrenia, Arch. Neurol. & Psychiat. **44**:1213 (Dec.) 1940.

2. Himwich, H. E.; Daly, C.; Fazekas, J. F., and Herrlich, H. C.: Effect of Thyroid Medication on Brain Metabolism of Cretins, Am. J. Psychiat. **98**:489, 1942.

3. Himwich, H. E., and Fazekas, J. F.: Cerebral Arteriovenous Oxygen Difference: I. The Effect of Age and Mental Deficiency, Arch. Neurol. & Psychiat. **50**:546 (Nov.) 1943.

per cent for 12 observations on children with mongolism 3 months to 5 years of age, and with the average value of 4.7 volumes per cent for 5 children with moderately severe hydrocephalus, from ½ year to 5 years of age.

Hydrocephalus and Microcephaly.—In only 1 of 6 patients with hydrocephalus was the arteriovenous oxygen difference significantly reduced (table 2) when age was taken into consideration (compare with table and figure of part I [3]). For that patient the cerebral arteriovenous oxygen difference was 2.2 volumes per cent in an observation made one day before the brain ruptured. Autopsy revealed that the thickness of the remaining cerebral cortex was reduced to 2 mm. For the 5 other patients with hydrocephalus the differences were what might have been expected at their ages. We have 4 observations on patients with primary microcephaly (table 2), i. e., with no apparent cause for the small size of the cranium

TABLE 2.—*Cerebral Arteriovenous Oxygen Differences for Children with Hydrocephalus and Microcephaly*

Hydrocephalus		Microcephaly	
Age	Arteriovenous Oxygen Difference, Vol. per Cent	Age	Arteriovenous Oxygen Difference, Vol. per Cent
Less than 1 year.........	2.2	5 years..................	4.1
Less than 1 year.........	4.6	8 years..................	3.1
Less than 1 year.........	4.8	15 years.................	6.2
3 years..................	4.4	22 years.................	6.5
5 years..................	3.8		
5 years..................	5.7		

TABLE 3.—*Average Cerebral Arteriovenous Oxygen Differences for Adults 20 Years of Age or Older*

Condition	Arteriovenous Oxygen Difference, Vol. per Cent
Normal..	6.7 (96)*
Undifferentiated mental deficiency.........................	6.6 (45)
Mongolism...	5.6 (30)
Cretinism...	5.5 (17)
Phenylpyruvic oligophrenia................................	5.5 (9)

* Numbers in parentheses indicate the number of observations from which the average values were obtained.

except insufficient growth of the brain. Their arteriovenous oxygen differences fell within normal limits for their ages.

Mongolism, Cretinism and Phenylpyruvic Oligophrenia.—In the first study [3] it was concluded that patients with undifferentiated mental deficiency possess cerebral arteriovenous oxygen differences like those of normal persons, and probably have a normal cerebral metabolic rate. In order to make easier comparisons with data previously obtained results for persons with mongolism, cretinism and phenylpyruvic oligophrenia have been reanalyzed on an age basis (table 3), similar to that of the patients with undifferentiated mental deficiency. Only in one age group, that of persons 20 years and more, were there sufficient data to justify comparison of all three types of mental deficiency. The average value of 6.6 volumes per cent for persons with undifferentiated mental deficiency was higher than the values for patients with mongolism, cretinism or phenylpyruvic oligophrenia. The average cerebral arteriovenous oxygen difference for 30 patients with mongolism between the ages of 20 and 45 was 5.6 volumes per cent. It was possible to study only 9 patients, between 20 and 37 years of age, with the rare disease of phenyl-

pyruvic oligophrenia. Their average cerebral arteriovenous oxygen difference was 5.5 volumes per cent. Reexamination of data previously presented on cretins revealed an average of 5.5 volumes per cent. Even though this is an average for only 6 persons, between the ages of 22 and 31, each subject, nevertheless, was examined more than once, on different days, and the average was that of 17 observations. When the Fisher t test was applied,[1] the differences between the values for persons with undifferentiated mental deficiency and the values for persons with mongolism and cretinism were significant, and the differences between the values for persons with undifferentiated mental deficiency and the values for persons with phenylpyruvic oligophrenia were probably significant. Data on persons with mongolism are available for a comparison of the effects of age on the cerebral arterio-

TABLE 4.—*Average Cerebral Arteriovenous Oxygen Differences for Persons with Mongolism or Undifferentiated Mental Deficiency*

Age, Yr.	Undifferentiated Mental Deficiency	Mongolism
Less than 10	4.7 (30)*	4.4 (21)
10 to 19	5.4 (55)	5.9 (17)
20 and over	6.6 (45)	5.6 (30)

* Numbers in parentheses indicate the number of observations from which the average values were obtained.

TABLE 5.—*Cerebral Arteriovenous Oxygen Differences for Persons with Various Forms of Mental Deficiency* *

Condition	Age, Yr.	No. of Observations	Average Cerebral Arteriovenous Oxygen Differences	Cerebral Metabolic Rate
Undifferentiated mental deficiency	20-55	45	6.6	Normal
Hydrocephalus, not terminal	Less than 1 to 5	5	Normal	Reduced
Microcephaly	5-22	4	Normal	Reduced
Mongolism	Less than 10	21	4.4	Reduced
	10-19	17	5.9	Reduced
	20 and over	30	5.6	Reduced
Cretinism	Over 20	17	5.5	Reduced
Phenylpyruvic oligophrenia	Over 20	9	5.5	Reduced
Hydrocephalus, terminal	Less than 1	1	2.2	Reduced
			Internal Jugular Vein	
Amaurotic familial idiocy	1-1½	6	5.7	
			Fontanel	
	1-1½	5	7.5	

* The values for cerebral arteriovenous oxygen differences are based on observations; the cerebral metabolic rates are estimated.

venous oxygen difference with the values for persons with undifferentiated mental deficiency. It is significant that the general pattern is the same as that for persons with undifferentiated mental deficiency, namely, one of increasing cerebral arteriovenous oxygen differences as age advances. There is, however, an important modification. Table 4 shows that the cerebral arteriovenous oxygen differences for persons with mongolism rise from the first to the second decade and then remain the same until old age. The increase in the cerebral arteriovenous oxygen difference, therefore, ceases ten years earlier for the patient with mongolism than for the patient with undifferentiated mental deficiency. Presumably, the increase in cerebral metabolism also stops at the earlier age. The data on the cerebral arteriovenous oxygen differences and on the cerebral metabolic rate are summarized in table 5.

4. Fisher, R. A.: Statistical Methods for Research Workers, London, Oliver & Boyd, 1928.

COMMENT

Amaurotic Familial Idiocy.—The arteriovenous oxygen difference which we have observed in patients with this condition was relatively high—higher than the values for patients with mongolism and hydrocephalus of approximately the same ages (tables 2 and 5). As we have stated, the children with familial idiocy were between the ages of 1 and 1½ years, and since we have no control experiments on normal babies between these ages, we could not say whether or not the values for the babies with familial idiocy deviated from the normal. We do suspect, however, that the children with amaurotic familial idiocy had a higher arteriovenous oxygen difference than normal, and from certain morphologic evidence[5] we believe that, despite this high oxygen difference, their metabolic rate was depressed. In this instance there appears to be no correlation between the arteriovenous oxygen difference and the cerebral metabolic rate; at least, no such claim can be made until further work is done along this line.

In the meantime, our belief that a child with amaurotic familial idiocy suffers from a depressed cerebral metabolic rate may be supported by certain biochemical and morphologic evidence. Here we find that the actively respiring gray matter is supplanted by a lipid material, substance X of Klenk,[6] which is probably relatively inert from the respiratory standpoint. It is well known that the metabolic rate of gray matter is much higher than that of white matter, presumably because of a higher concentration of respiratory enzymes in the former.[5d] The distribution of the lipid matter in the brain in a case of amaurotic familial idiocy may explain the reason for the smaller arteriovenous difference for blood drawn from the internal jugular vein than for that collected from the fontanel. According to Hassin,[5a] though the abnormal accumulation of lipids may occur diffusely throughout the entire central nervous system, it is especially obvious in the optic thalamus. Such a differential distribution of pathologic changes may account for a lower utilization of oxygen in the blood collected from the internal jugular vein, which represents the return flow from the entire organ, including the optic thalamus, than from the fontanel, which contains the venous blood coming chiefly from the cerebral hemispheres.

Hydrocephalus.—The low oxygen consumption of the patient who died with extreme hydrocephalus must be regarded as a result of destruction of brain tissue and as indicative of an impaired cerebral metabolic rate. Unless such destruction is extensive, however, no decrease of the cerebral arteriovenous oxygen difference is observed, a condition presented by the 5 other patients with hydrocephalus. If these 5 patients had a depressed cerebral metabolism, the cerebral blood flow must have slowed to maintain the arteriovenous oxygen difference.

Microcephaly.—If the usual relationship existed between the cerebral arteriovenous oxygen difference and the cerebral blood flow in the patients with microcephaly, their cerebral metabolic rate per gram of brain was not depressed. Because of the reduction of cerebral tissue, however, the total metabolism of the brain may have been less than normal.

5. (*a*) Hassin, G. B.: Histopathology of the Peripheral and Central Nervous System, Philadelphia, William Wood & Company, 1933, p. 315. (*b*) Klenk, E.: Ueber die Natur der Phosphatide der Milz bei der Niemann-Pickschen Krankheit, Ztschr. f. physiol. Chem. **229**:151, 1934; (*c*) Ueber die Natur der Phosphatide und anderer Lipoide des Gehirns und der Leber bei der Niemann-Pickschen Krankheit, ibid. **235**:24, 1935. (*d*) Holmes, E. G.: Oxidations in Central and Peripheral Nervous Tissue, Biochem. J. **24**:914, 1930.

6. Klenk (footnote 5 *b* and *c*).

Mongolism, Cretinism and Phenylpyruvic Oligophrenia.—There is no reason to suspect an accelerated cerebral blood flow in the patients with mongolism, cretinism or phenylpyruvic oligophrenia, and it may even have been reduced in association with the first two diseases. If the cerebral blood flow was either normal or slow in all patients with these disorders, then the diminished arteriovenous oxygen differences indicate a subnormal cerebral metabolic rate. In these three groups of patients the mental deficiency was probably associated with an inadequate elaboration of cerebral energy.

The low cerebral metabolism of the patients with mongolism may be explained by degenerative processes in the cerebral gray matter. Morphologic studies revealed that such persons exhibit degeneration of brain tissue, loss of nerve cells and atrophy of the cortex.[7] These differences between persons with mongolism and normal persons are most pronounced after 19 years of age as indicated by failure of the cerebral arteriovenous oxygen difference to rise after that period. The increase in concentration of cerebral enzymes which occurs as growth proceeds is arrested ten years earlier in the person with mongolism than in the normal person. Evidence presented by Benda [7b] is in agreement with this conclusion of the early arrest in growth and development of the brain in association with mongolism.

In cretins, as in mongolism, a low cerebral metabolic rate may be attributed to an inadequate development of cerebral enzymes. It is thought that thyroxin stimulates the metabolic rate by increasing the concentration of enzymes, an effect exerted directly on the protein moiety of the enzyme.[8] In athyrotic cretins the subnormal cerebral metabolism may therefore be ascribed to a diminished concentration of respiratory enzymes. The cause of the depression of cerebral metabolism in patients with phenylpyruvic oligophrenia is unknown. It is recognized, however, that such patients lack the enzyme necessary for the oxidation of phenylalanine.

CONCLUSIONS

The cerebral arteriovenous oxygen differences are high in patients with amaurotic familial idiocy and normal for those with microcephaly and hydrocephalus not in the terminal stages.

Above the age of 20 years the cerebral arteriovenous oxygen difference is lower for patients with mongolism, cretinism and phenylpyruvic oligophrenia than for persons with undifferentiated mental deficiency.

In persons with mongolism the cerebral arteriovenous oxygen difference ceases increasing ten years earlier than in those with undifferentiated mental deficiency.

It is suggested that cerebral metabolism is reduced in patients with mongolism, cretinism, phenylpyruvic oligophrenia, advanced hydrocephalus, microcephaly and amaurotic familial idiocy.

Albany Medical College.

7. (*a*) Meyer, A., and Jones, T. B.: Histological Changes in the Brain in Mongolism, J. Ment. Sc. **85**:206, 1939. (*b*) Benda, C. E.: The Central Nervous System in Mongolism, Am. J. Ment. Deficiency **45**:42, 1940. (*c*) Holmes.[5d]

8. Klein, J. R.: Nature of the Increase in Activity of the D-Amino Acid Oxidase of Rat Liver Produced by Thyroid Feeding, J. Biol. Chem. **131**:139, 1939.

CEREBRAL CORTEX OF A MAN WITH SENILE DEMENTIA BELIEVED TO BE 107 YEARS OLD[1]

W. RIESE, M.D.
RICHMOND, VA.
AND
I. S. ZFASS, M.D.
WILLIAMSBURG, VA.

Among the numerous publications dealing with the morphologic and histologic characteristics of the senile brain there are a few scattered cases of very old brains (Simchowicz,[2] Gellerstedt[3] and others). The study of these specimens, however, was included as part of a more general investigation of old brains, without particular attention to the detailed consideration of the very old brain. The results of the present studies corroborated the general observations that have been made on old brains. As far as we know, there are only 2 specimens of brains (Kuczynski[4] and Aksel[5]) obtained from persons more than 100 years of age on which such monographic studies, based on appropriate methods,[6] have been made. None of the aforementioned reports, however, deals with the problems of cortical organization which we shall consider in this study. In accordance with the more or less predominant cell type in a given area, von Economo and Koskinas[7] distinguished areas of pyramidization, granularization and spindlization. These three types of cortical organization characterized the adult brain. Little is known about their formation in the course of cortical development. In general, the embryonic and the infantile brain is richer in "granular" cells than the adult brain. From the viewpoint of

1. It is true that the statement of the patient could not be verified objectively, but this holds true for the very small number of cases of persons over 100 years of age submitted to a systematic study by previous authors. We feel that there is no obvious reason to doubt the patient's own statement, his psychiatric picture at the time he made his statement suggesting no depersonalization or any evidence of delusions or disorientation with regard to his own person. But even if this were true, he would still have been a very old man, and the neuropathologic observations would still have to be interpreted as those pertaining to a very old brain. The observations, therefore, would lose nothing of their value as first statements of their kind.

2. Simchowicz, T.: Histologische Studien über die senile Demenz, in Nissl, F., and Alzheimer, A.: Histologische und histopathologische Arbeiten über Grosshirnrinde, Jena, Gustav Fischer, 1910-1911, vol. 4, p. 267.

3. Gellerstedt, N.: Zur Kenntnis der Hirnveränderungen bei der normalen Altersinvolution, Uppsala, Almqvist & Wiksell, 1933.

4. Kuczynski, M. H.: Von den körperlichen Veränderungen bei höchstem Alter, Krankheitsforschung 1:85-163, 1925.

5. Aksel, I. S.: Ueber das Gehirn des "ältesten Mannes der Welt" (Zaro Aga), Arch. f. Psychiat. 106:260-266, 1937.

6. For general bibliography concerning very old brains, see: Critchley, M.: Ageing of the Nervous System, in Cowdry, E. V.: Problems of Ageing, Baltimore, Williams & Wilkins Company, 1939, pp. 483-500.

7. von Economo, C., and Koskinas, G. N.: Die Cytoarchitektonik der Hirnrinde des erwachsenen Menschen, Berlin, Julius Springer, 1925.

comparative neurology it is noticeable that, according to Abbie,[8] granularization is already present in the monotreme cortex, whereas the same author could not detect pyramidization in this primitive mammalian species. One of us (W. R.)[9] observed all the three types of cortical organization in Macropus, a highly specialized marsupial (Diprotodontia). Nothing is known about the behavior of these types of cortical organization in old age and in very old age, no attention having been given to this problem by previous investigators.

REPORT OF A CASE

History.—J. H., an unmarried white man, was born in Ireland. He stated that he was 29 years of age two years before Lee's surrender, which would have made him 107 years of age at the time of his death on Nov. 3, 1941.

He came to this country at the age of 18 years; he worked as a farmhand and lived alone until his admission to the Eastern State Hospital, on Sept. 23, 1930. He was supported by the county prior to his commitment to the hospital, which was necessitated by his irritability, insomnia, wandering, loss of memory, silly conduct and suspiciousness.

During his residence at the hospital he was for the most part quiet and well behaved but occasionally became irritable and pugnacious. He exhibited characteristic symptoms of a psychosis of the organic reaction type and of senile deterioration, which was progressive, terminating in a bedridden, vegetative state.

Physical Examination.—The patient was of small stature, with pronounced dorsal kyphosis and scoliosis to the right. He was fairly well nourished. There was evidence of severe peripheral arteriosclerosis. The heart and lungs were normal. The blood pressure was 140 systolic and 90 diastolic. There was slight generalized tremor, which became more noticeable on occasions. The left pupil was once recorded as being smaller than the right; it reacted sluggishly to light and in accommodation. Neurologic examination otherwise revealed nothing abnormal. The patient became progressively weaker physically and was bedridden for about one month before his death.

Postmortem Examination.—General Gross Observations: The subject was fairly well nourished and did not appear to be over 60 years of age. The lungs weighed 360 Gm. each and showed a few scattered healed, calcified tuberculous lesions and a small cavity measuring 2 cm. in diameter in the apex of the left lung. The weight of the heart was 320 Gm. There were a fibrous epicardial plaque on the anterior wall of the right ventricle and moderate fibrosis of the myocardium. The mitral leaflets showed calcification, with partial stenosis. The aortic leaflets were slightly thickened. The coronary vessels showed considerable tortuosity, with moderate arteriosclerotic changes but no occlusion. The first portion of the aorta was free from atheromatous changes, but the transverse, thoracic and abdominal portions showed severe arteriosclerotic changes, with calcification and ulceration. The liver was small, weighed 980 Gm. and had a dark brownish, mottled appearance. The gallbladder was normal. The spleen weighed 80 Gm., and the pulp was semisolid. The pancreas and the adrenals were normal. The right and left kidneys weighed 100 and 85 Gm. respectively. The capsules stripped with slight difficulty, a diffusely granular surface with many small surface cysts remaining. The renal architecture was disturbed; the cortical striations were indistinct. The bladder, the prostate and the testicles were normal. There was a small hydrocele on the right. The esophagus, the stomach and the small intestine were normal. The mucosa of the cecum and colon showed what appeared to be small, superficial areas of ulceration. The sigmoid and rectum appeared normal.

Microscopic Examination of the Organs (Dr. M. L. Dreyfus, Clifton Forge, Va.): The gross pathologic observations were confirmed by the microscopic studies, which revealed the following changes: interstitial fibrosis of the myocardium; fibrous thickening of the epicardium; arteriosclerosis of the aorta; arteriosclerosis of the kidneys; fibrocaseous pulmonary tuberculosis; chronic pulmonary emphysema; functioning testicles (complete spermato-

8. Abbie, A. A.: Cortical Lamination in the Monotremata, J. Comp. Neurol. **72:**429-467, 1940; The Excitable Cortex in Parameles, Sarcophilus, Dasyurus, Trichosurus and Wallabia (Macropus), ibid. **72:**469-487, 1940; Cortical Lamination in a Polyprotodent Marsupial, Perameles Nasuta, ibid. **76:**509-536, 1942.

9. Riese, W.: The Cellular Structure of the Marsupialian Cortex, Naturaliste canad., to be published.
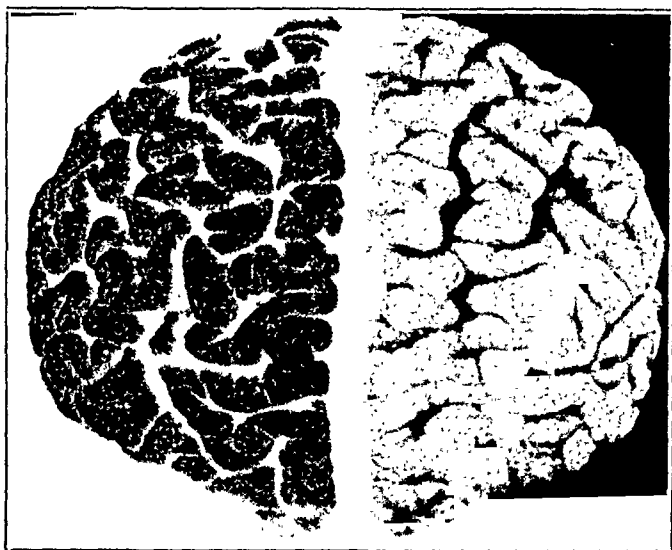
Fig. 1.—Frontal lobes of the brain, showing slight convolutional atrophy.
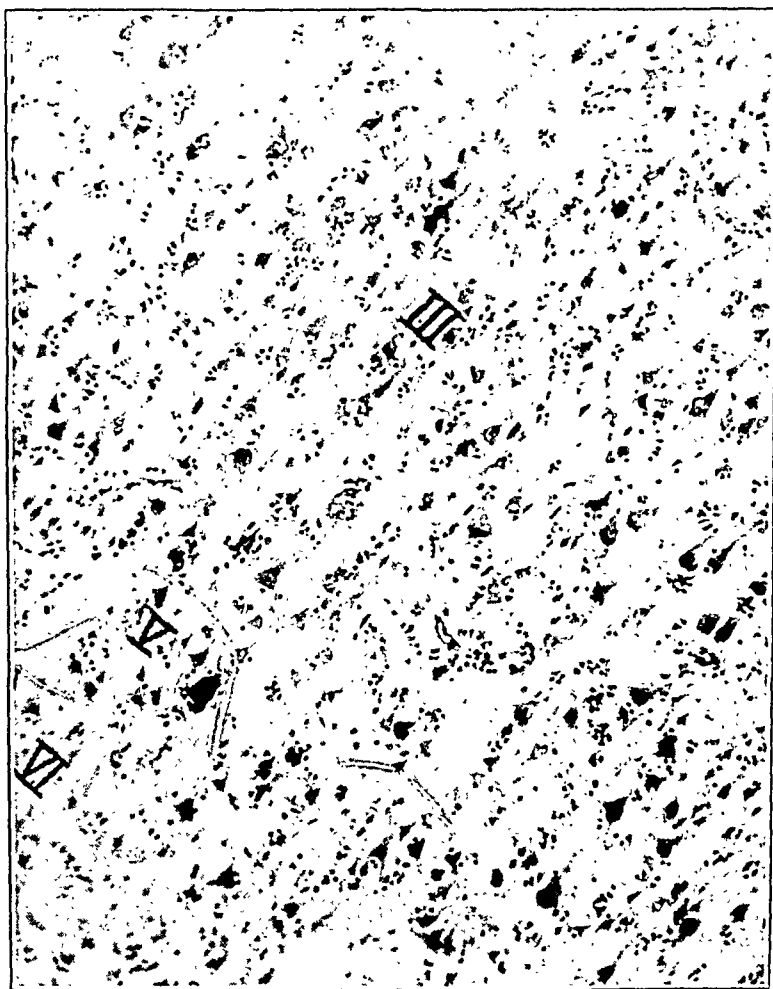
Fig. 2.—Area FA of von Economo, showing pyramidization; × 190.

genesis); brown atrophy of and fatty changes in the liver, and atrophy of the spleen. No signs of regeneration were noted in any of the organs. The normal, as well as the abnormal, observations did not differ from what may be noted in any elderly person, but the complete spermatogenesis was remarkable.

Gross Examination of the Brain: The brain weighed 1,280 Gm. The vessels at the base showed moderate arteriosclerotic changes. There was slight convolutional atrophy, limited to the anterior regions of the frontal lobe (fig. 1). Coronal sections through various levels of the brain revealed only slight internal hydrocephalus. No other gross neuropathologic changes were seen.

Histologic Examination of the Brain: The following areas of the cortex were examined: FA, FB, FE, TC, PB, PC, OC, LA, HD and IB.[10] In all these areas the general cyto-architecture was well preserved, and the various regional variations of the cortical lamination
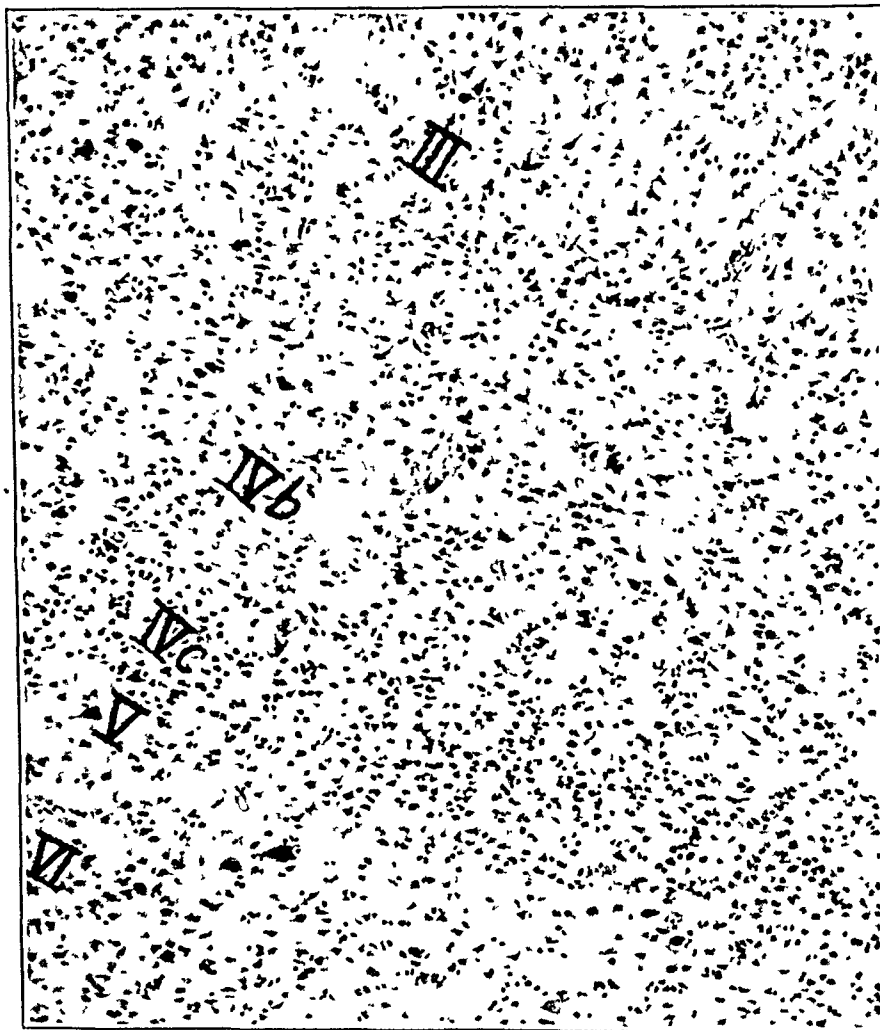
Fig. 3.—Area OC of von Economo, showing granularization; × 190.

could easily be identified. The same held true for the various types of cells. Definite pyramidization was to be seen in area FA, granularization in areas OC and TC and spindlization in area LA (figs. 2, 3 and 4). Thus, the structural characters of the cortex, its regional variations, as well as the three processes of pyramidization, granularization and spindlization, had undergone no change in this very old brain. The brain showed all the characteristics of a senile brain: cellular changes, gliosis, neurofibrillary alterations (Alzheimer type) and senile plaques (neurofibrillary changes and senile plaques however, were lacking in the cerebellar cortex). The cellular changes were of only moderate degree, and they did not lead to complete destruction or formation of so-called blanks in the cytoarchitectural picture. The cellular changes consisted of fatty degeneration, loss of distinct outlines, chromatolysis and increase

10. Terminology of von Economo and Koskinas.[7] The first letter in these designations indicates the lobe to which a given cortical area belongs

in staining properties and eccentricity of the nucleus. These cellular changes seemed to be less pronounced in the koniocortex. However, the intensity of the cellular changes did not seem to be related to the size of the cell, the giant cells of the fifth layer of area FA being well preserved, whereas the large elements of the third, fourth and fifth layers of area OC were, in their turn, particularly involved. The glial reaction was intense. It consisted of so-called neuronophagia (involving not only the deep but the middle layers and in some instances —area FA—the whole section), perivascular gliosis, formation of glial symplasms and glial turfs. This glial reaction was much more pronounced in the areas of pyramidization than in those of granularization and spindlization. Only a small amount of intracellular pigment was noted. There was intense and generalized proliferation of the vessels throughout the white
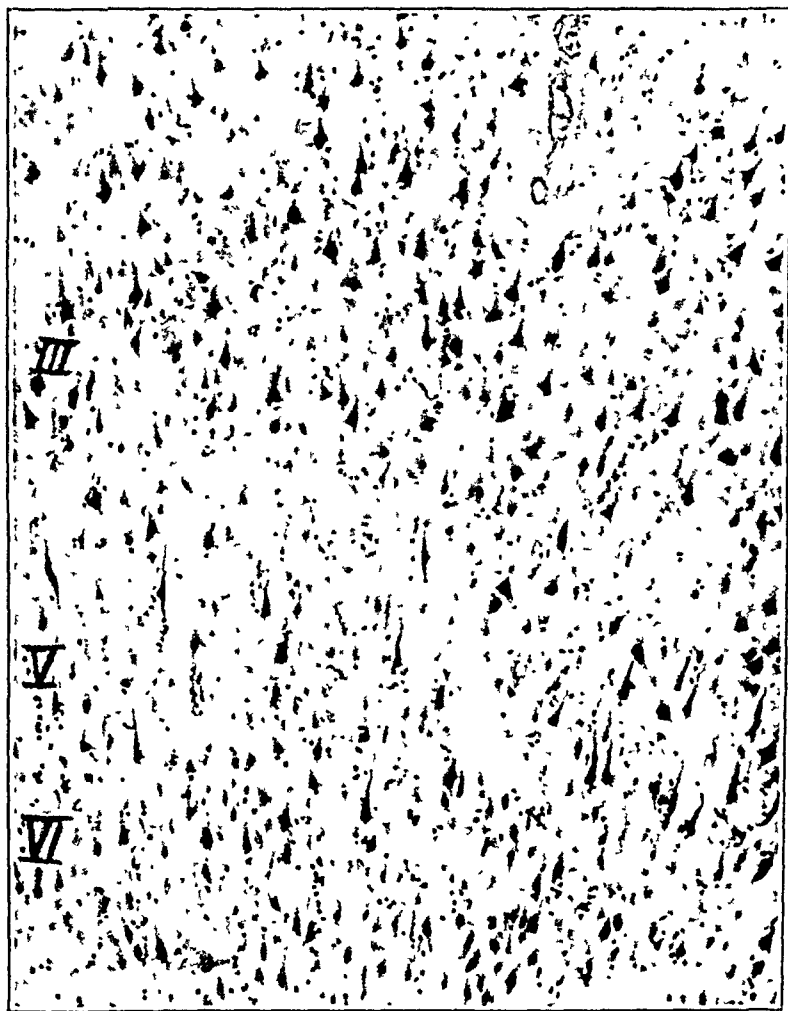
Fig. 4.—Area LA of von Economo, showing spindlization; × 190.

matter, which showed a cribriform state. There were also thickening and hyaline degeneration of the capillary wall and capillary fibrosis. Binucleated ganglion cells were noted in areas FA, FB and LA. Microscopic areas of softening were seen in areas OC and LA; they revealed an excellent glial and mesenchymal organization. There was disseminated demyelination in the white matter of all cortical areas and in the cerebellum. *Plaques fibromyéliniques* could be seen in area FA and in the cerebellar cortex.

COMMENT

This very old brain was remarkable for the minimal degree of cortical (frontal) atrophy. Similar observations have been made by previous investigators on senile

brains (Grünthal,[11] Gellerstedt,[3] Aksel[5] and Rothschild[12]). The brain of a 107 year old man described here showed the well known histopathologic changes observed in senile persons irrespective of the presence of senile dementia. The cellular changes, however, could be considered only as moderate, and this is interesting not only because of the advanced age of the patient but because of the existence of a clinical picture of senile dementia for eleven years. The cytoarchitecture was intact and revealed the typical regional variations in all their integrity. Furthermore, the three processes of pyramidization, granularization and spindlization were obvious. The same held true for an 87 and a 91 year old brain studied recently by us, and this answers for the first time (and in a negative way) the question submitted by von Economo and Koskinas as to the possible change of the cytoarchitectural pattern in function of old age. Finally, this very old brain showed also a notable tendency to repair (mesenchymal and glial), and even regeneration (if such was the significance of binucleated ganglion cells and *plaques fibromyéliniques*). In this connection, it might be interesting to recall that Kuczynski,[4] observed typical signs of regeneration in the liver and pancreas of a man over 100 years of age. Further studies will have to show whether the regional variations in the degree of cellular changes and glial repair, both of which were much more striking in the areas of pyramidization than in the areas of granularization and spindlization, were merely individual features of this very old brain. Although previous investigators (Gellerstedt[3] and others) could not discover any constant areal variations in the intensity of cellular changes in senile brains, more notable cellular changes in area FA were also observed by us in the aforementioned brains of persons aged 87 and 91 years. This problem requires further investigation. In general, the very old brain reveals signs not only of disintegration but of new integration, and this may be a neurologic contribution to a revision of the traditional conception of old age.

SUMMARY

1. The cytoarchitecture in this very old brain was well preserved and revealed the well known regional variations.

2. There were definite pyramidization, granularization and spindlization.

· 3. The gross and histopathologic changes generally considered as characteristic of the senile brain were present to only a moderate degree.

4. Processes of repair and regeneration were detectable.

Medical College of Virginia, Richmond, Va.

Eastern State Hospital, Williamsburg, Va.

---

11. Grünthal, E.: Die pathologische Anatomie der senilen Demenz und der Alzheimerschen Krankheit, in Bumke, O., and Förster, O.: Handbuch der Geisteskrankheiten, Berlin, Julius Springer, 1930, pp. 638-672.

12. Rothschild, D.: Pathologic Changes in Senile Psychoses and Their Psychobiologic Significance, Am. J. Psychiat. **93**:757-788, 1937.

Clinical, Technical and Occasional Notes

SENSORY RECEPTION IN HYSTERICAL ANESTHESIA AS MEASURED BY THE COLD PRESSOR RESPONSE

CAPTAIN J. D. SULLIVAN, MEDICAL CORPS, ARMY OF THE UNITED STATES

The paradox of hysterical anesthesia consists of failure to perceive sensory stimuli despite intact and functioning innervation. The preservation of deep and superficial reflexes and the nonanatomic distribution of the anesthesia furnish evidence of the neurologic integrity of the affected parts. The psychodynamic features reveal the conversion nature of the symptoms.

The cold pressor test consists of a standard cold stimulus applied to an extremity as a procedure for quantitative estimation of the reactivity of the vasomotor system.[1] The response consists of an increase in systemic blood pressure on immersion of a limb in cold water. It has been demonstrated previously that the cold pressor response depends on the transmission of sensation through intact peripheral nerves.[2]

This study was undertaken to determine whether conscious perception of the stimulus is necessary to cause an elevation of blood pressure, or whether the reaction is the result of reflexes mediated at a lower level of integration.

METHOD

With the patient in a sitting position, the basal blood pressure is established after five or six readings. One extremity is then immersed in ice cold water for exactly one minute. It is usually possible to take three or four readings during the period of immersion. The normal response consists of elevation of the systolic and diastolic pressures, which may vary considerably but always occurs in the presence of intact innervation. There is a return to the basal level in a minute or two after withdrawal of the limb. The procedure is repeated on the opposite limb. Either the normal or the anesthetized limb may be used first without alteration of the results.

CASE MATERIAL [3]

Three patients with complete hysterical anesthesia of a foot, and 1 patient with anesthesia of one hand were studied. The part immersed was insensible to pain or cold. No discomfort or inclination to withdrawal was demonstrated while the anesthetic limb was being tested, and this was sharply in contrast to the emotional display when the contralateral extremity was immersed.

SUMMARY AND CONCLUSIONS

Four patients with a hysterically anesthetized limb showed a cold pressor response in the affected limb despite the denial of subjective sensations of pain or cold.

The cold pressor response of the affected limb was in all subjects similar to that of the normal limb.

Subjective perception of pain and cold is not necessary for completion of the cold pressor response.

---

1. Hines, E. A., and Brown, G. E.: A Standard Stimulus for Measuring Vasomotor Reactions, Proc. Staff Meet., Mayo Clin. **7**:322-335 (June 8) 1932.

2. Sullivan, J. D.: Dependence of the Cold Pressor Reaction on Peripheral Sensation, J. A. M. A. **117**:1090-1091 (Sept. 27) 1941.

3. The first 2 patients were studied at the Station Hospital at Fort Eustis, Va., in October 1942; the other 2 patients were in the neuropsychiatric service of the Station Hospital, Fort Jackson, S. C., in January 1943.

Further evidence indicates that hysterical anesthesia does not block sensory stimuli at the lowest segmental levels.

These observations suggest that the cold pressor response may be useful in differentiation of hysterical and peripheral nerve anesthesias.

CASE 1.—K. R. had hysterical monoplegia with anesthesia of the right leg. The basal blood pressure was 118 systolic and 80 diastolic; the cold pressor response in the left leg was 128 systolic and 86 diastolic and in the right leg 124 systolic and 84 diastolic.

CASE 2.—A. A. had hysterical hemiplegia of the right side, with anesthesia of the right side of the face, the right arm and the right side of the trunk.

The basal blood pressure was 120 systolic and 90 diastolic; the cold pressor response on the left side was 130 systolic and 98 diastolic and on the right side 130 systolic and 98 diastolic.

CASE 3.—B. J. had hysterical palsy of the right leg, with rigidity and anesthesia.

The basal blood pressure was 130 systolic and 84 diastolic; the cold pressor response in the left leg was 140 systolic and 90 diastolic and in the right leg 145 systolic and 90 diastolic.

CASE 4.—C. O. had paralytic residuals of poliomyelitis, with hysterical anesthesia in the right leg.

The basal blood pressure was 132 systolic and 90 diastolic; the cold pressor response in the left leg was 140 systolic and 98 diastolic and in the right leg 150 systolic and 98 diastolic.

News and Comment

THE AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY, INC.

The following certifications were made in December 1943:

Psychiatry.—By Examination: Helen Benczur, New York; Courtenay L. Bennett, Tampa, Fla.; Martin A. Berezin, Fort Meade, Md.; Leo Berman, Boston; Eric L. Berne, Brentwood, N. Y.; Nathan Blackman, Fort Leavenworth, Kan.; L. D. Borough, Fort Sill, Okla.; Lester L. Burtnick, Camp Carson, Colo.; John Melton Cotton, Jackson, Miss.; * Francis M. Forster, Philadelphia; Bernhardt S. Gottlieb, New York; John Edward Harty, Williamsburg, Va.; Elmer Haynes, Madison, Wis.; Margaret Hohenberg, New York; William T. Hyslop, Traverse City, Mich.; Mildred H. January, Hartford, Conn.; Henriette R. Klein, New York; Sidney D. Klow, Denver; Alan A. Lieberman, Elgin, Ill.; Elizabeth MacDougall, Winnetka, Ill.; James D. Mahoney, Norristown, Pa.; Johann Rudolf Marx, Ingleside, Neb.; * Charles I. Oller, Philadelphia; William L. Pious, Byberry, Philadelphia; * Theodore Rothman, Paterson, N. J.; Sidney Rubin, New York; Bertram Schaffner, Camp Gordon, Ga.; Lazarus Secunda, Indiantown Gap, Pa.; * Isaac Shapiro, Schenectady, N. Y.; Maurice D. Spottswood, Bethesda, Md.; Wolfgang M. F. Sulzbach, Waverly, Mass.; Morris J. Tissenbaum, Norwich, Conn.; Herbert A. Wiggers, New York, and Isadore Zfass, Carlisle, Pa.

On Record: Kilian K. Bluhm, New York; Edgar L. Braunlin, Dayton, Ohio; * Fred P. Currier, Grand Rapids, Mich.; Royal George Grossman, Camp Atterbury, Ind.; Samuel W. Hartwell, Snyder, N. Y.; George E. Hesner, New Orleans; Merrill Olmstead Parker, Auburn, N. Y., and Melvin John Rowe, Norwalk, Calif.

Neurology.—By Examination: * Louis S. Chase, Westover Field, Mass.; Joseph F. Dorsey, New Haven, Conn.; * Maurice H. Greenhill, Durham, N. C.; Solomon Lesse, Newport, R. I.; Richard L. Masland, Randolph Field, Texas; * Bernard C. Meyer, New York; * Bernard L. Pacella, New York; * Nathan N. Root, Brooklyn; * Sidney Rosenbliett, Westover Field, Mass.; * Siman Stone, Manchester, N. H.; * Ellsworth H. Trowbridge Jr., Camp Joseph T. Robinson, Ark., and * Carel van der Heide, Chicago.

On Record: Gabriel Steiner, Detroit.

Neurology and Psychiatry.—By Examination: Earl Hay Adams, New York; Andrew Russell Anderson, Atlanta, Ga.; Charles M. Holmes, Orangeburg, N. Y.; Heinz Lichtenstein, Buffalo; Else Pappenheim, New York; Eugene Pumpian-Mindlin, Fort McClellan, Ala.; Leo Rangell, Sheppard Field, Texas; Victor H. Rosen, Fort Jackson, S. C.; Gabriel A. Schwarz, Philadelphia; Isidor Silbermann, New York; John Edmund Skogland, New Orleans; Heyman Smolev, San Luis Obispo, Calif., and Samuel Yochelson, Camp Kilmer, N. J.

On Record: Andrew B. Jones, St. Louis, and Paul Loewy, New York.

---

* The asterisk denotes complementary certification.

DEPARTMENT OF PSYCHIATRY, McGILL UNIVERSITY

McGill University announces the creation of a department of psychiatry and, in association with the Royal Victoria Hospital, the establishment of an institute for research and teaching. Through the generosity of Sir Montagu and Lady Allan, a building and an extensive site have been provided.

. The institute will contain fifty beds for patients suffering from early and acute psychiatric conditions. Facilities for intensive treatment are being set up. The development of research and treatment will be major objectives, and, with this in view, large and well equipped laboratories are to be provided.

The project is being supported both by the Rockefeller Foundation and the government of the Province of Quebec. Dr. D. Ewen Cameron has been appointed to the chair of psychiatry and will also be the director of the institute.

Abstracts from Current Literature

Anatomy and Embryology

DEVELOPMENT OF THE HUMAN MESENCEPHALIC TRIGEMINAL ROOT AND RELATED NEURONS.
WILLIAM F. WINDLE and JAMES E. FITZGERALD, J. Comp. Neurol. **77**:597 (Dec.) 1942.

Windle and Fitzgerald studied the brain stems of human embryos at the 4 to the 7 week stage and the brain stems of cat embryos at comparable stages. The material was prepared for fiber study. Motor and sensory roots of the trigeminal nerve began to develop during the fourth week of gestation. During the early part of the fifth week the sensory root fibers of the trigeminal nerve entered the metencephalon opposite the sulcus limitans. .The ascending fascicles merged with the lateral longitudinal tract. This composite tract began at the isthmus and descended into the tegmentum of the myelencephalon. The motor root of the trigeminal nerve coursed through bundles of the lateral longitudinal tract medial to the sensory root. The mesencephalic root arose as part of the lateral longitudinal tract. Probst's tract arose in common with the mesencephalic root in the metencephalon. Its fibers could be differentiated from the mesencephalic root only by observing their origin from smaller, less argyrophilic, cells and their course caudal to the trigeminal nerve, where they lay medial to the spinal tact of the trigeminal nerve in the lateral longitudinal tract. ADDISON, Philadelphia.

THE NUMERICAL RELATION BETWEEN THE GANGLION CELLS OF THE RETINA AND THE FIBERS
IN THE OPTIC NERVE OF THE DOG. L. B. AREY and M. GORE, J. Comp. Neurol. **77**:609 (Dec.) 1942.

Arey and Gore counted the ganglion cells in the retinas of 4 dogs, the sections having been stained with Ehrlich's hematoxylin, without a counterstain. The nerve fibers in 4 optic nerves were counted after the nerves had been treated with silver. The animals ranged in weight from 2.5 to 37 Kg. The number of ganglion cells in the retina varied from 149,320 to 192,160. The smallest retina had the greatest relative concentration of ganglion cells and vice versa. The total number of fibers in the optic nerve ranged from 152,360 to 164,920. The ratio of ganglion cells to nerve fibers was approximately 1:1. ADDISON, Philadelphia.

DEVELOPMENT OF THE CRANIAL SYMPATHETIC GANGLIA IN THE CAT. ELIZABETH J. COWGILL
and WILLIAM F. WINDLE, J. Comp. Neurol. **77**:619 (Dec.) 1942. .

Cowgill and Windle studied the development of the cranial sympathetic ganglia in 34 cat embryos. The embryos had a crown-rump length of from 3 or 4 to 60 mm. They were prepared by the pyridine-silver method. The cranial sympathetic ganglia are derived from neuroblasts which have migrated from the sensory ganglia of the fifth, seventh and ninth cranial nerves along nerve bundles. The ciliary ganglion was recognized at the 5.5 mm. stage as a distinct bud of cells protruding forward from the ophthalmic portion of the semilunar ganglion. At the 8 mm. stage a few cells had arrived at the site of the ganglion. The sphenopalatine ganglion was recognized at the 6 mm. stage by a migration of neuroblasts along the maxillary nerve. At the 7 mm. stage cells were seen to migrate from the geniculate ganglion along the greater superficial petrosal nerve. At the 11 mm. stage some cells had arrived at the site of the ganglion. The otic ganglion was recognized at the 7 mm. stage by a migration of cells from the semilunar ganglion along the mandibular nerve. At the 9 mm. stage migration was also occurring along the lesser superficial petrosal nerve. The earliest migration of the submaxillary ganglion was seen along the mandibular nerve at the 7 mm. stage. Migration was complete at the 15 mm. stage. ADDISON, Philadelphia.

THE NUMBER OF MYELINATED AND UNMYELINATED FIBERS IN THE OPTIC NERVE OF VERTE-
BRATES. S. R. BRUESCH and L. B. AREY, J. Comp. Neurol. **77**:631 (Dec.) 1942.

Bruesch and Arey determined the total fiber content of the optic nerves of thirty-three representative vertebrates. Portions of nerves from the same animal were treated with osmium tetroxide or with silver. All the fibers in hagfish and brook lamprey were unmyelinated. All

the fibers in the dogfish, shark pup, guitar fish, sting rat, shovel-nosed sturgeon, bowfin, goldfish, bullhead, duckling, chick, pigeon, dog, cat, rabbit, gray rat, guinea pig, sheep, macaque and man were myelinated. The opossum, bat and albino rat had respectively 33, 44 and 21 per cent of unmyelinated fibers.

<div align="right">Addison, Philadelphia.</div>

Size, Development and Innervation of Labyrinth Sensory Areas in Squalus. William B. Freedman and Roland Walker, J. Comp. Neurol. **77**:667 (Dec.) 1942.

Freedman and Walker studied the size, development and innervation of the sensory area in the ears of a series of 22 dogfish. The approximate areas were determined by measurement and calculations from serially sectioned specimens. The sensory area was not sufficiently differentiated for measurement until the 48 mm. stage. In the 580 mm. specimen the sensory area, though immature, totaled 18 sq. mm. for one ear, as compared with 11 sq. mm. for the human ear. The total sensory area for one ear increased thirty times, while the body length increased twelve times.

<div align="right">Fraser, Philadelphia.</div>

Cytoarchitecture of Individual Parietal Areas in the Monkey (Macaca Mulatta) and the Distribution of the Efferent Fibers. Talmage L. Peele, J. Comp. Neurol. **77**:693 (Dec.) 1942.

Peele ablated individual parietal areas or areas 1, 2, 5 and 7 together in 9 young macaque monkeys, after demarcating the areas by electrical stimulation. The excised cortex was prepared for cell study. After three weeks the brains were removed. Blocks from each level of the spinal cord were prepared by the Marchi technic. The parietal cortex showed six well developed cell layers throughout, but the development of certain cell layers varied from one area to another. All the parietal areas sent association fibers to the adjacent cerebral lobes. All sent commissural fibers to the contralateral areas, to the homolateral pontile nuclei and to the thalamic nuclei—the lateralis posterior, the ventralis posterolateralis and the ventralis posteromedialis. Area 5 sent some fibers to the nucleus medialis dorsalis of the thalamus. All areas sent fibers through the pyramid to the spinal cord, where they accompanied the corticospinal tracts to the same and to the opposite side. Crossed fibers from all areas except 7 could be found at lumbar levels, but uncrossed fibers only from area 3 reached this level. Uncrossed fibers from other areas terminated at the cervical levels. Areas 3 and 5 sent fibers to the substantia nigra; areas 5 and 7, to the pretectal region, and area 7, to the superior colliculus.

<div align="right">Addison, Philadelphia.</div>

Transynaptic Effect of Neonatal Axon Section on Bouton Appearance About Somatic Motor Cells. Melvin Schadewald, J. Comp. Neurol. **77**:739 (Dec.) 1942.

Schadewald removed segments of the right sciatic and femoral nerves high in the thigh in a series of newborn kittens. In a second series the contents of the right orbit were removed. The animals were killed at the age of 21, 28, 60 or 90 days. The regions of the nuclei of the trochlear and abducens nerves and of the lumbosacral segments of the spinal cord of all animals were studied by means of silver impregnation. *Boutons terminaux* were not seen about the anterior horn cells in the newborn or in the young kittens. They were noted in the nuclei of the trochlear and abducens nerves at the postnatal age of 3 weeks and on the anterior horn cells of the lumbosacral segments of the spinal cord at the age of 4 weeks. Axonal section altered neither the time of appearance nor the number of *boutons* which appeared about somatic motor cells.

<div align="right">Addison, Philadelphia.</div>

The Early Development of the Motor Cells and Columns in the Spinal Cord of the Sheep. Donald H. Barron, J. Comp. Neurol. **78**:1 (Feb.) 1943.

Barron studied 22 sheep embryos ranging in length from 5.5 to 44 mm. and in age from 21 to 40 days. The spinal cords were prepared with silver technics. At the 22 day stage the roof and floor plates are formed, and the sulcus limitans and the mantle layer are present. A primary grouping of neuroblasts is seen as early as the twenty-first day. By the thirty-fourth day the lateral mass of neuroblasts has given rise to ventrolateral, dorsolateral, central and retrodorsal groups. Baron finds that the motor cell columns in the anterior cervical and brachial segments of the cord are all laid down at the time the embryo first becomes active. At that time the cell columns are in their final position, but their development is incomplete.

<div align="right">Fraser, Philadelphia.</div>

Physiology and Biochemistry

STUDIES OF THE B VITAMINS IN THE HUMAN SUBJECT: IV. MENTAL CHANGES IN EXPERIMENTAL DEFICIENCY. HARRIET E. O'SHEA, K. O'SHEA ELSOM and RUTH V. HIGBE, Am. J. M. Sc. **203**:388 (March) 1942.

O'Shea, Elsom and Higbe undertook to measure objectively the psychologic status of the adult human subject receiving an experimental diet deficient in the B vitamins. Psychologic tests were administered to 4 voluntary subjects taking an experimental diet and to 4 normal controls who consumed an adequate diet. Each subject consumed a diet which supplied an adequate quantity of all dietary factors except the B vitamins. There were three experimental periods: (1) the period when the subjects received the experimental diet alone; (2) the period when thiamine hydrochloride was added to the diet, and (3) the period when the vitamin B complex (brewers' yeast or synthetic vitamin B complex) was administered. Each subject and each control were subjected to four psychologic test series. The special mental functions studied were speed of coordination of the hand muscles, intelligence, reasoning ability (reading), foresight and judgment, prose memory and visual and auditory memory. The subjects succeeded less well in solving the mazes when deficient in the B vitamins than after receiving thiamine hydrochloride or the vitamin B complex. There was a definite relation between the degree of deficiency and the degree of impairment of maze performance. The results indicated that an impaired maze performance is a significant manifestation of deficiency of the B vitamins. No significant differences were observed in intelligence test scores during deficiency or after therapy, indicating that adult intelligence test performance does not deteriorate during deficiency of the B vitamins nor does it improve after therapy with these substances. Reasoning ability (reading) and speed of hand muscle coordination (tapping) showed no measurable deterioration when the subjects were deficient in the B vitamins and no improvement after therapy with thiamine hydrochloride or with the vitamin B complex.   MICHAELS, Boston.

INDEPENDENT DIFFERENTIATION OF THE SENSORY AREAS OF THE AVIAN INNER EAR. HIRAM J. EVANS, Biol. Bull. **84**:252, 1943.

Differentiation of the sensory areas of the avian inner ear has been studied by transplantation of isolated primordia of the inner ear to the chorioallantoic membrane. Maculas, cristae and a papilla basilaris differentiated in the transplants. The sensory areas of the transplanted labyrinths are comparable to those of the control. The morphogenesis of the membranous labyrinth was greatly suppressed in the grafts, but the histogenesis of the sensory components showed little retardation. Since the sensory areas of the inner ear undergo typical development when isolated from their nerve supply, Evans concludes that they are capable of differentiating independently of the nervous system.   COBB, Boston.

ACID-SOLUBLE PHOSPHORUS COMPOUNDS OF CEREBRAL TISSUE. WILLIAM E. STONE, J. Biol. Chem. **149**:29, 1943.

Analysis of cerebral tissue after fixation in situ with liquid air seems to offer the nearest presently available approach to the chemical composition of the brain in the living animal. Studies of acid-soluble phosphorus compounds by this method have demonstrated the presence of inorganic phosphate, phosphocreatine, adenosine triphosphate and possibly guanosine triphosphate. There still remains a quantity of organic acid-soluble phosphorus compounds which have not been chemically identified. An improved method is presented for the fractionation of the acid-soluble phosphorus compounds of cerebral tissue. A procedure is described for the determination of the ribose component of the nucleotides. The unidentified organic acid-soluble phosphorus compounds of cerebral tissue include at least three distinct substances: (a) one which behaves like hexose-6-monophosphate; (b) one which is thought to be aminoethyl phosphate, and (c) an ethanol-soluble substance. Attempts to detect the presence of phosphoglycerate, triose phosphate and phosphopyruvate in cerebral tissue were unsuccessful. The principal changes observed to occur during thirty minutes of postmortem autolysis of cerebral tissue are the hydrolysis of phosphocreatine and the partial decomposition of adenosine triphosphate. The methods used indicate the presence of adenosine diphosphate, adenylic acid, a nucleoside or free pentose and inorganic phosphate among the decomposition products of adenosine triphosphate.   PAGE, Indianapolis.

PITRESSIN DIAGNOSIS OF IDIOPATHIC EPILEPSY. W. BLYTH, Brit. M. J. **1**:100 (Jan. 23) 1943.

Blyth describes a method of precipitating convulsive seizures in patients who claim to have or are suspected of having idiopathic epilepsy. It is of particular value with patients

whose attacks occur at infrequent intervals. The rationale of the method is based on the fact that retention of water in the body will precipitate the seizure in predisposed persons but will affect normal persons but little. Retention of water is obtained by the oral administration of copious amounts of water, together with intramuscular injection of pitressin. The method is contraindicated in the presence of diabetes, nephritis, arteriosclerosis or myocarditis. Blyth used the procedure with 87 patients suspected of having idiopathic epilepsy, the diagnosis for 86.6 per cent of whom was verified by the test.   ECHOLS, New Orleans.

AN ACTION OF ADRENALIN ON TRANSMISSION IN SYMPATHETIC GANGLIA, WHICH MAY PLAY A PART IN SHOCK. EDITH BÜLBRING and J. H. BURN, J. Physiol. **101**:289, 1942.

Bülbring and Burn studied the transmission of nerve impulses in sympathetic ganglia in eviscerated dogs in which the sympathetic ganglia were perfused. In small amounts epinephrine augmented the transmission of impulses in the ganglia but depressed it in large amounts.

In atropinized cats small doses of epinephrine augmented the ganglionic action of acetylcholine, but larger doses depressed it. In a spinal cat the pressor effect of splanchnic stimulation was increased by continuous perfusion of epinephrine, but single large doses depressed the response. This depression was accompanied by a fall in the general blood pressure. The authors express the opinion that the latter action may occur in certain cases of shock.

                                                                                THOMAS, Philadelphia.

THE EFFECT OF VARIATIONS IN THE SUBARACHNOID PRESSURE ON THE VENOUS PRESSURE IN THE SUPERIOR LONGITUDINAL SINUS AND IN THE TORCULAR OF THE DOG. T. H. B. BEDFORD, J. Physiol. **101**:362, 1942.

Contrary to the conclusions previously reached by Becht and by Weed and Flexner, Bedford finds that any considerable increase in subarachnoid pressure is accompanied by a decrease in venous pressure in the superior longitudinal sinus and in the torcular.

A rapid increase in subarachnoid pressure from the pressure level of the cerebrospinal fluid to 500 mm. of isotonic solution of sodium chloride was invariably accompanied by a fall in venous pressure, which averaged 20 mm. of isotonic solution of sodium chloride. The fall in venous pressure was less when the subarachnoid pressure was elevated more slowly; for example, it fell on an average about 10 mm. when the subarachnoid pressure was elevated at the rate of 100 mm. per minute. The venous pressure returned to normal when the subarachnoid pressure was lowered to its original level.   THOMAS, Philadelphia.

EFFECT OF BONE DYSPLASIA ON CRANIAL NERVES IN VITAMIN A-DEFICIENT ANIMALS. E. MELLANBY, J. Physiol. **101**:408, 1943.

When young dogs are brought up on diets deficient in vitamin A and carotene, local overgrowth of certain bones of the skull causes compression, twisting and lengthening of most of the cranial nerves, some of which show extensive degenerative changes. The destructive changes are chiefly confined to the sensory nerves, the motor cranial nerves for the most part escaping. Motor nerves often suffer compression, lengthening and twisting as a result of overgrowth of bone, but show no degeneration.

In the experiments described, the nerves most affected were the cochlear and vestibular divisions of the eighth cranial nerve, especially the former; the first and second branches of the fifth cranial nerve and the second and first cranial nerves. Apparently, the reason for the greater susceptibility of the sensory nerves lies in the compression not only of the nerve fibers but of the ganglia.

Degeneration in the optic nerve may be produced in vitamin A–deficient animals not only by direct pressure of overgrown bone and by increased intracranial pressure but by a primary degenerative change, beginning in the retina itself. The early optic nerve atrophy associated with bleaching of the tapetum is probably a direct effect of the vitamin A deficiency on retinal cells.

In experiments in which the calcium intake was high the increased growth of certain bones appeared to be due to formation of an excess of cancellous tissue.

                                                                                THOMAS, Philadelphia.

SYNTHESIS OF ACETYLCHOLINE IN SYMPATHETIC GANGLIA AND CHOLINERGIC NERVES. W. FELBERG, J. Physiol. **101**:432, 1943.

Sympathetic ganglia, such as the superior cervical ganglion, and cholinergic nerves, such as the cervical portion of the sympathetic trunk, the vagus and phrenic nerves and the motor

roots, if divided with scissors into small pieces and incubated for one to two hours in buffered saline solution containing physostigmine, are still able to synthesize acetylcholine. This property is lost if the nerves are ground with silica. Sensory nerve roots yielded no acetylcholine on extraction and failed to synthetize it under conditions which gave evidence of synthesis when motor nerves were used.

When the cervical part of the sympathetic trunk is cut in a preliminary operation, the distal part of the nerve and the superior cervical ganglion lose their property of synthesizing acetycholine after about forty-eight hours. This loss precedes the loss of nerve conduction. In the ganglion it coincides with the time when synaptic transmission becomes impaired and lost. Felberg concludes that synthesis of acetylcholine in sympathetic ganglia is a property of the preganglionic endings and is a necessary preliminary to normal, particularly sustained, synaptic transmission.

THOMAS, Philadelphia.

SYNAPTIC POTENTIALS AND TRANSMISSION IN SYMPATHETIC GANGLION. J. C. ECCLES, J. Physiol. **101**:465, 1943.

When synaptic transmission through a sympathetic ganglion is blocked by curare, stimulation of the preganglionic fibers sets up a local negative potential of the ganglion cells in relation to their axons. Eccles terms this the synaptic potential, and he states that it spreads decrementally along the postganglionic fibers. After an initial rapid rise, it reaches a flat-topped summit at ten to twenty milliseconds and decays slowly.

In these respects the synaptic potential resembles a catelectrotonic potential and thus is analogous to the end plate potential of curarized muscle. Summation of the synaptic potentials is set up by two preganglionic volleys. If the summated potential is high enough, the ganglion cells discharge impulses. The bearing of these results on the theories of synaptic transmission is discussed.

THOMAS, Philadelphia.

Psychiatry and Psychopathology

ONE HUNDRED CASES OF INDECENT EXPOSURE. ALEX J. ARIEFF and DAVID B. ROTMAN, J. Nerv. & Ment. Dis. **96**:523 (Nov.) 1942.

Arieff and Rotman analyze 100 unselected cases of sexual exhibitionism, the most common sex offense seen at the Psychiatric Institute of the Municipal Court of Chicago. All the offenders were males, and the peak age was in the third decade. Only 4 patients were Negroes. The offense almost invariably occurred at home or in a public place, and a majority exposed themselves in broad daylight. As a whole, the patients were of low economic and cultural status. Sixty-two persons were single and 38 married; thus marriage, obviously, does not constitute a cure for the condition. Most of the exhibitionists had been previously arrested on various charges. The authors divide the patients into two groups: (1) institutional, made up predominantly of mentally defective, schizophrenic and senile persons, and (2) noninstitutional, composed of persons with psychopathic conditions, compulsive neuroses, borderline mental deficiencies and schizoid states. Previous sexual irregularity was frequent. The authors believe that the offense is evidence of severe personality maladjustment. They regard the act as an asocial aberration of the socially acceptable exhibitionism which is a preliminary stage of mating.

CHODOFF, Langley Field, Va.

PHYSICAL, PSYCHIATRIC AND PSYCHOMETRIC STUDIES OF POST-ENCEPHALITIC PARKINSONISM. DONALD SHASKAN, HELEN YARNELL and KAREN ALPER, J. Nerv. & Ment. Dis. **96**:652 (Dec.) 1942.

Twenty-seven patients with postencephalitic parkinsonism were treated with large doses of an alkaloid of the atropine group, little difference being noted whether atropine, scopolamine or stramonium was used. Since factors other than the effect of the drug were thought to be important, psychiatric and psychologic studies were carried out. The patients studied psychiatrically gave histories of an insecure childhood. They had poorly adjusted personalities and tended to find a satisfactory adjustment in their illness. Two patients with oculogyric crises showed compulsive phenomena, in agreement with the observations of Jelliffe. A group subjected to a battery of psychologic tests showed a considerable degree of reduction in intellectual efficiency. The most notable defects were slowness of association, difficulty in performing mental shifts, inability to organize parts into a simple gestalt unit and specific failing of memory. Drawings of a man were interpreted as illustrating either sexual preoccupation or intellectual impairment. Rorschach records showed that all patients made some effort to

adjust to their disabilities. Narrowing of the range of interests, anxiety, depression and sensitivity to body disability were all prominent in the Rorschach records.

CHODOFF, Langley Field, Va.

A COMPARISON OF SCHIZOPHRENIA AND MANIC-DEPRESSIVE WITH REFERENCE TO EMOTIONAL MATURITY. M. A. DUREA, J. Nerv. & Ment. Dis. **96**:663 (Dec.) 1942.

Persons with schizophrenia surrender to difficulty by regressing, while patients with manic-depressive disorders surrender but do not regress. The degree of emotional maturity attained is a fundamental factor in both conditions. Durea attempts to appraise this factor by the use of the interest-attitude test of Pressey with a group of patients with manic-depressive psychoses, a group with schizophrenia and a control group. With this method both the pathologic groups were inferior in emotional age to the control group, but the median scores for the schizophrenic patients (except in one subtest) were lower than those for the manic-depressive patients. Schizophrenic patients were most retarded emotionally according to test II (worries) while manic-depressive patients were most retarded according to test IV (admirations). The author suggests that emotional retardation is a function of the tendency to regression.

CHODOFF, Langley Field, Va.

CRYPTIC NOSTALGIA. C. L. WITTSON, H. I. HARRIS and W. A. HUNT, War Med. **3**:57 (Jan.) 1943.

In the usual cases of nostalgia the subject shows a mild reactive depression, with mild retardation, agitation and tearfulness. He has insight into the cause of his feelings. The authors describe another type which is met with in the armed services. The soldier is apathetic, absent-minded, slow in responding, inattentive and unable to concentrate and fails to carry out routine duties. He seems preoccupied. He apparently has adjusted to his new environment adequately. He fails even to notice that there is something wrong with him and has no insight into its cause. Such a state may be confused with schizophrenia or with feeblemindedness because sometimes the patient does poorly in a psychometric examination.

Psychiatric interview reveals that the patient is preoccupied constantly with thoughts and memories of home. The condition is not homesickness but a fixation on home and family. It is possible usually to give him insight into his condition, which generally clears up entirely as a result of a single interview.

PEARSON, Philadelphia.

Diseases of the Brain

EPIDEMIOLOGIC ASPECTS OF ENCEPHALITIS IN YAKIMA VALLEY, WASH. W. M. HAMMON and B. F. HOWITT, Am. J. Hyg. **35**:163 (March) 1942.

From the inductive epidemiologic analysis of 86 cases of encephalitis in human beings and of 20 cases of encephalomyelitis in horses in 1939 and 1940, it appears to Hammon and Howitt that both the western equine virus and the St. Louis virus were present in Yakima Valley simultaneously and produced some instances of mixed infection. Neutralization tests of the blood serum of 50 patients showed 84 per cent to be positive for the western equine virus, 72 per cent for the St. Louis virus and 56 per cent for both viruses. The serum from 75 closely comparable controls from the general population disclosed neutralizing antibodies for the western equine virus in 6.7 per cent, for the St. Louis virus in 28 per cent and for both in 2.7 per cent. The figures for patients and controls were compared with those obtained for serum from other areas in the West, and the difference helped to establish the presence of the St. Louis virus in the serum of Yakima patients as etiologically significant. The serum of a few normal chickens, pheasants and a duck were found to neutralize the western equine virus, and the blood of some horses neutralized the St. Louis virus. Suggestive correlation was found between the occurrence of antibodies in patients only to the St. Louis virus and contact with, or proximity to, horses, an observation which may be significant, since antibody to this virus was found in horses.

J. A. M. A.

CLINICAL AND ELECTROENCEPHALOGRAPHIC OBSERVATIONS IN SEVERE EPILEPSY UNDER TREATMENT. DOUGLAS GOLDMAN, Am. J. M. Sc. **205**:388 (March) 1943.

Goldman reports the result of a study of 16 patients with severe epilepsy for from two months to three years with the aid of electroencephalograms during determination of the effects of medication, chiefly with diphenylhydantoin sodium and phenobarbital. Most of the patients were inmates of a state hospital for mental illness whose psychoses were manifestations of the convulsive disorder. In every instance the protocols which accompanied the electro-

encephalogram revealed that the tracing was correlated with the clinical evidence. The author concludes that adequate, vigorous and, above all, sustained treatment of convulsive disorders in their early stages, preferably under electroencephalographic control, may restore patients to complete freedom from seizures and protect them from late sequelae, such as psychoses.

MICHAELS, Martinsburg, W. Va.

CHOREA COMPLICATING POLYCYTHEMIA VERA. LAURENCE M. KOTNER and JOHN H. TRITT, Ann. Int. Med. 17:544 (Sept.) 1942.

Kotner and Tritt report the case of a white woman aged 64 with chorea and polycythaemia vera, the fifth case of the kind to be reported and the first instance in the literature in which autopsy was performed on a person with such a condition. Thrombi were observed only in the smaller veins of the brain, with no predilection for localization in the basal ganglia or in the area immediately adjacent to them. Both cerebral hemispheres showed widespread involvement. The xanthochromic and bloody appearance of spinal fluid obtained shortly before death was explained by a small hemorrhagic area in the choroid plexus of the fourth ventricle.

PRICE, Philadelphia.

SYPHILIS OF THE CENTRAL NERVOUS SYSTEM. CLEMSON MARSH, Bull. Los Angeles Neurol. Soc. 7:182 (Dec.) 1942.

Marsh reports a study of 145 cases of neurosyphilis in which the disease was verified at autopsy; a disagreement between the clinical and the pathologic diagnosis was often noted. The most common errors in diagnosis were due to (1) incomplete study of the patient because of sudden death; (2) failure to recognize the minimal signs of chronic meningeal syphilis; (3) inaccurate classification of well defined cases of neurosyphilis, and (4) tendency to make a general diagnosis of neurosyphilis .without differentiation of the form.

The author states that the various types of neurosyphilis are still proved pathologically to be fairly clearcut entities and that in most cases the patient should present fairly definite clinical symptoms. A diagnosis of a combined type of neurosyphilis, such as dementia paralytica, tabetic form, generally is wrong, the symptoms being due usually to multiple vascular lesions or to a syphilitic entity plus some other disease.

LESKO, Bridgeport, Conn.

LOSS OF EMOTIONAL EXPRESSION AND BODY SCHEME. ARNOLD P. FRIEDMAN and J. M. NIELSEN, Bull. Los Angeles Neurol. Soc. 7:206 (Dec.) 1942.

Friedman and Nielsen report 3 cases in which there were illusion of absence of a minor limb and loss of ipsilateral emotional expression. They believe that this syndrome may be due to a deep lesion close to the thalamus.

LESKO, Bridgeport, Conn.

DISORIENTATION AND ASSOCIATED GERSTMANN SYNDROME FROM INTRACEREBRAL HEMORRHAGE. ARTHUR M. PETTLER and AIDAN A. RANEY, Bull. Los Angeles Neurol. Soc. 7:207 (Dec.) 1942.

Pettler and Raney report a case of a waitress aged 39 in whom a convulsion suddenly developed on the right side and a subarachnoid hemorrhage was noted. A short time later right homonymous hemianopsia, amnesic aphasia, alexia, agraphia, acalculia, disorientation and "finger agnosia" developed, and operation revealed a subcortical hematoma in the lower parietal and the posterior temporal region on the left side. After operation she continued to show the same mental defects as before.

LESKO, Bridgeport, Conn.

ACUTE CARDIO-VASCULAR COLLAPSE AFTER INSULIN SHOCK TREATMENT. ANDRÉ A. WEIL, J. Nerv. & Ment. Dis. 96:556 (Nov.) 1942.

Weil reports a case in which, shortly after the termination of insulin coma, there occurred an acute cardiovascular collapse, with cessation of heart action. Two ampules of epinephrine hydrochloride (1:1,000) injected into the heart at fifteen second intervals produced resumption of the heart beat and recovery. Cardiac changes during hypoglycemia are due both to increased venous return to the right side of the heart and to a central release of parasympathetic function secondary to cerebral anoxemia. Despite this, few cardiovascular accidents have been reported during shock treatment, although cardiac and pulmonary failures have both been mentioned. The occurrence of the symptoms in Weil's case after the coma had been terminated by carbohydrates is attributed to a reactive rise in the insulin and epinephrine levels, with their subsequent effects. In spite of this, the case illustrates that at least in some instances intracardiac administration of epinephrine is a life-saving measure.

CHODOFF, Langley Field, Va.

A New Pyramidal Sign of Great Frequency. Lane Allen and Hervey Cleckley, J. Nerv. & Ment. Dis. 97:146 (Feb.) 1943.

In an attempt to elicit from the toes a reflex comparable to the Hoffmann sign of the hand, Lane and Cleckley have discovered a new sign of disease of the pyramidal tract which they believe to occur frequently. With the leg relaxed and the foot in slight plantar flexion, the second toe is flicked sharply upward with the finger applied to the ball of the toe. A positive result is indicated by a quick and transient dorsiflexion of the great toe and sometimes of the lesser toes. The maneuver is similar to that described by Rossolimo and sometimes elicits the Rossolimo reflex. The new sign, referred to as hallux extension, is extremely sensitive and may appear with slighter impairment of function of the pyramidal tract than is necessary to produce the Babinski or the Rossolimo sign. The authors suggest that the new sign may result from damage to area 6, and that it is an early and very sensitive, although not absolute, indication of pyramidal dysfunction.

Chodoff, Langley Field, Va.

A Case of Cerebellar Atrophy. Mogens Ellermann, J. Nerv. & Ment. Dis. 97:389 (April) 1943.

Ellermann reports the case of a man aged 65 who, at the age of 4½ years, sustained a severe injury to the head, followed by behavior difficulties and failure of mental development. Between the ages of 35 and 40 signs of cerebellar disease gradually appeared, with ataxic gait, intention tremor and dysarthria. At about the age of 44 he was hospitalized with an atypical and grandiose type of psychosis, later marked by psychic dissolution. Pneumoencephalographic examination revealed pronounced cerebellar atrophy. In view of the late development of the cerebellar syndrome, a traumatic origin was considered unlikely. Because of the purity of the cerebellar picture, the case is classed as one of abiotrophy, probably a primary parenchymatous atrophy of the cortex of the type first described by Marie, Foix and Alajouanine.

Chodoff, Langley Field, Va.

Cerebellar Extradural Hematoma. F. K. Kessel, J. Neurol. & Psychiat. 5:96 (July-Oct.) 1942.

Kessel reports the case of a woman aged 24 who sustained an injury to the back of her head, followed by unconsciousness and vomiting. After a lucid interval of thirty hours, in which only severe headache was experienced, cerebellar fits suddenly set in, followed by deepening unconsciousness. Roentgenograms showed only slight separation of the left half of the lambdoid suture. A cerebrospinal fluid block was demonstrated. An extradural hematoma was encountered over the left cerebellar hemisphere, the hemorrhage originating from rupture of the left transverse sinus. The hematoma was evacuated and the cisterna opened wide to relieve the increased intracranial pressure. Complete recovery followed. The author believes that the cerebellar fits represented a special form of decerebrate rigidity and may have resulted from disturbed intracranial circulation. Isolated extradural cerebellar hematoma is extremely rare and, according to the author, is always due to laceration of the transverse sinus or one of its tributary veins. It is usually accompanied by fracture of the skull. The low pressure within the transverse sinus may account for the slow development of the hematoma. The lesion frequently presents a diagnostic problem, which is rendered less difficult when cerebellar fits are present. Unless the condition is recognized early, the prognosis is usually bad.

Malamud, Ann Arbor, Mich.

Fatal Intracranial Venous Haematoma Following Ventricular Drainage. J. Schorstein, J. Neurol. & Psychiat. 5:142 (July-Oct.) 1942.

Schorstein reports 3 cases in which death resulted from intracranial hemorrhage following ventricular drainage. In all 3 cases chronic internal hydrocephalus with increased intracranial pressure was present, caused in 2 instances by obstruction of the aqueduct near its commencement and in the third case by adhesive arachnoiditis blocking the foramen of Magendie. In the first 2 instances the hemorrhage was extradural, while in the third it was subdural and intracerebral. The bleeding was probably of venous origin, derived from the rupture of dural veins. In all 3 cases the extracerebral clots overlay the frontal lobes. The author attributes the hemorrhages to the reduction of intracranial pressure by the ventricular drainage. This decreased pressure causes the dura to become detached from the bone and, aided by traction on the dura by way of the venous anchorage of the brain, results in rupture of veins passing between the dura and the skull. The venous pressure, which exceeds the cerebrospinal fluid pressure when drainage is instituted, aids still further the expansion of the clot from the ruptured veins. Young persons with chronic hydrocephalus are the ones most likely to have a complication.

Malamud, Ann Arbor, Mich.

ABSCESS WITHIN THE SELLA TURCICA SIMULATING PITUITARY TUMOR: SURGICAL CURE. H. J. SVIEN and J. G. LOVE, Proc. Staff Meet., Mayo Clin. **17**:497 (Sept. 23) 1942.

Isolated reports of metastatic abscess in the sella turcica are known, but primary abscess of the pituitary is rare. So far as Svien and Love are aware, no cases of the latter have been recorded. Their patient, a woman aged 34, complained of headache and vomiting. At the age of 21, five months after the birth of a child, her menses ceased, and immediately after the birth of her child diabetes insipidus developed, which was relieved temporarily by solution of posterior pituitary U. S. P. This condition became less severe during the four years preceding entrance into the hospital. There developed severe pain in the left side of the head, which extended from the left eye into the neck and was associated with blurred vision, nausea and vomiting. For several months she had noticed loss of vision in the left field. Examination revealed normal fundi and bitemporal hemianopsia. The sella turcica was observed to be enlarged. A diagnosis of a chiasmal lesion was made; a transfrontal craniotomy was performed, and an abscess, occupying the sella turcica, was encountered. About 15 cc. of pus was aspirated, and sulfanilamide crystals were placed within the abscess cavity and sprinkled around the optic nerves and the chiasm. No growth was obtained from the pus. Convalescence was uneventful save for the development of left hemiplegia and hemianesthesia on the seventh postoperative day. This disappeared spontaneously in several days. The fundi remained normal, and the visual fields returned to normal. No focus for the' abscess was determined.

ALPERS, Philadelphia.

PARAPHYSIAL CYSTS OF THE THIRD VENTRICLE. LAURENCE M. WEINBERGER and BENJAMIN BOSHES, Surgery **13**:368, 1943.

Weinberger and Boshes report a case of paraphysial cyst of the third ventricle successfully removed at operation, it being the seventeenth instance thus far recorded in which surgical recovery resulted. The patient was a woman aged 22 with a history of headache and vomiting for three weeks. Some weeks after operation the patient recalled that the headaches were associated with changes in posture, being either caused or intensified by her assuming a recumbent position. Neurologic examination on her admission to the hospital revealed merely a high degree of papilledema and palsy of both external rectus muscles. Localization was determined by ventriculographic means, both lateral ventricles were greatly dilated, and air was not visualized in the third ventricle. Both intraventricular foramens were sharply cut off. Operation was performed through a right frontal osteoplastic bone flap and a transcortical incision into the right lateral ventricle. The tumor was removed by drawing it through the foramen of Monro into the lateral ventricle, where its attachment to the choroid plexus was coagulated and cut. The patient made a good postoperative recovery, marred only by transient left hemiparesis and a jacksonian seizure on the left side five days after operation. Four months later she was entirely well, and the neurologic status was normal.

The authors point out that there is no syndrome typical of tumors of this kind, but it is often recorded that headache is noticeably affected by changes in position of the head, the so-called ball valve phenomenon. Diagnosis is dependent on the evidence afforded by pneumography.

SHENKIN, Philadelphia.

OSTEOCHONDROMAS ARISING FROM THE BASE OF THE SKULL. CARL FELIX LIST, Surg., Gynec. & Obst. **76**:480, 1943.

List reports 7 cases of osteochondroma of the skull, the tumor in 5 being primarily intracranial, arising from the sphenoid bone, and in 2 primarily extracranial, arising from the ethmoid or sphenoid region, with secondary intracranial extension. All the primary osteochondromas originated from the sphenoid bone and extended intracranially into the posterior parasellar region. One of them was but the intracranial manifestation of generalized chondromatosis. The characteristic site of the tumors makes it probable that they develop from residuals of the cartilaginous primordial cranium. The author notes that chordomas are found in a location similar to that of osteochondromas, viz., at the junction of the basisphenoid and the basiocciput.

Osteochondroma is usually seen in young adults and grows slowly; hence a course of over ten to twenty years is not unusual. Intracranial osteochondroma produces a neurologic syndrome characteristic of its parasellar location. A primarily extracranial osteochondroma produces symptoms at first characteristic of an expansive or obstructive lesion of the paranasal sinuses. Later, as the tumor penetrates the cranial cavity, the optic nerve is first involved, and later a parasellar syndrome may be produced. Roentgenograms are almost pathognomonic.

The treatment is surgical. The prognosis is good, providing malignant change in the tumor has not occurred. Recurrence ultimately results, however, since only partial removal is possible at operation.

SHENKIN, Philadelphia.

EFFECT OF PNEUMOENCEPHALOGRAPHIC TESTS ON EPILEPSY AS PROVED BY ELECTROENCEPHALO-GRAMS. RICARDO MOREA and JOSE B. ODORIZ, Rev. neurol. de Buenos Aires 7:207 (July-Sept.) 1942.

Morea and Odoriz report 3 cases of epilepsy in which electroencephalographic studies were made before and after injection of air into the lumbar subarachnoid space. In all 3 cases the electroencephalographic patterns were typical of grand mal. In 2 of the cases clinical improvement followed pneumoencephalographic study, the electroencephalographic tracings in both cases reverting to normal or near normal. In the third case there was no improvement, either clinical or electroencephalographic. The authors conclude that pneumoencephalography is of definite value as a therapeutic measure in the management of epilepsy.

PIETRI, New York.

ENCEPHALITIS FOLLOWING INCLUSION CONJUNCTIVITIS. F. BAMATTER, Confinia neurol. 4:314, 1942.

Bamatter reports 3 cases of encephalitis occurring in association with inclusion conjunctivitis in newly born infants. There were associated inflammatory hydrocephalus and albuminocytologic dissociation in the cerebrospinal fluid. The author states that while it has not been proved that keratoconjunctivitis with inclusion bodies and encephalitis in such infants have a common etiologic factor, the associated clinical manifestations are striking. He believes that this variety of encephalitis constitutes a clinical entity which has not been hitherto described.

DEJONG, Ann Arbor, Mich.

Peripheral and Cranial Nerves

THE PROBLEM OF PRIMARY SCIATIC NEURITIS: AN ANALYSIS OF 55 CASES. B. J. ALPERS, H. S. GASKILL and B. P. WEISS, Am. J. M. Sc. 205:625 (May) 1943.

Alpers, Gaskill and Weiss, impressed with the inconsistencies in the literature, reviewed their cases of sciatic neuritis in order to establish the incidence of sciatic neuritis and to determine its differentiation from other types of sciatica. Of 55 patients, 37 (67 per cent) were males and 18 females. All but 4 of the males were engaged in heavy work; most of the females were housewives. The age incidence varied from 16 to 72 years, the majority of the patients (41, or 73 per cent) being between the ages of 30 and 60. Pain referable to the hip or leg of one side was the presenting symptom of the majority of patients. Pain in the back was present only in 17 (30 per cent) of the patients; it is more common with secondary sciatica. In 3 patients pain in the leg was bilateral; in all the others it was unilateral. The location of the pain in the leg varied widely. In 29 patients the pain extended from the thigh, in the region of the hip, to the ankle, toes or heel. The pain in 29 patients lasted from one to twelve weeks, in 9 patients from three to six months and in 13 patients from one to five years. The patients, 13 (23 per cent), in whom it persisted for one year or more had recurrent attacks of sciatic neuritis. Mere prolongation of symptoms does not indicate a secondary cause of the sciatica unless other evidence, such as roentgenographic changes in the vertebrae and increased protein in the spinal fluid, is present.

Only 7 of the 55 patients had paresthesias. None had incontinence of the bladder or rectum. Tenderness of the nerve was found in 46 of 55 patients, and it was usually noted everywhere along the sciatic trunk. Lasègue's sign was absent in only 7 patients. The achilles reflex was decreased or absent on the side of the neuritis in 36 patients. Muscular weakness was not encountered. Sensory changes occurred in only a few patients, with a slight decrease in pain sensation over the lateral aspect of the thigh or leg. Foci of infection constituted one of the outstanding causes and included diseased tonsils (28 patients), carious teeth (20 patients), sinusitis (12 patients) and prostatitis (8 patients). Osteoarthritis of the sacroiliac joint or of the lumbar vertebrae was observed in 17 patients. Of diagnostic importance is tenderness of the nerve trunk, particularly in the sciatic notch and the popliteal space; this symptom was present to some degree in every patient. Severe tenderness of the nerve trunk was noted in 22 patients, moderate tenderness in 24 patients and mild tenderness in 9 patients. The authors believe that true sciatic neuritis is not rare.

MICHAELS, Martinsburg, W. Va.

ALBUMINOCYTOLOGIC DISSOCIATION IN THE SPINAL FLUID WITH XANTHOCHROMIA. KARL O. VON HAGEN, Bull. Los Angeles Neurol. Soc. **7**:198 (Dec.) 1942.

Von Hagen reports 2 cases of infectious neuronitis (Guillain-Barré syndrome) with xanthochromia. The cases are of interest because xanthochromia has been reported to be of unusual occurrence in cases of infectious neuronitis.   LESKO, Bridgeport, Conn.

FACTORS AFFECTING RECOVERY OF MOTOR FUNCTION AFTER NERVE LESIONS. E. GUTMANN, J. Neurol. & Psychiat. **5**:81 (July-Oct.) 1942.

Recovery of the motor function of a muscle begins with its reinnervation but is complete only after a series of steps in the process of "functional completion" have taken place. To test this, Gutmann crushed the peroneal nerve at the knee in rabbits and observed the gradual recovery of ability to spread the toes. He found that new axons returned to the muscle in ten days, contraction of the muscle on stimulation of the nerve in eighteen to twenty days, the first reflex function in twenty-five days and full reflex function eight days later. The circumference of the denervated muscle began to increase and its threshold to direct stimulation to decrease before reflex function, and sometimes even before direct excitability, returned. After reappearance of reflex function fibrillation continued in the muscles for about two weeks; the normal weight of the muscle was regained about twelve weeks afterward.

The following factors influence the recovery of function: 1. The level of the lesion. The time between the beginning of functional recovery of the muscle and its completion is greater the more distant the lesion from the muscle, but the rate of nerve regeneration remains fairly constant and does not depend on the level of the lesion. 2. The type of injury. Recovery is slower after severance and suture than after crushing of a nerve, even if the latter is carried out over a distance of 4 cm. This may be due to slower advance of the process of regeneration and the shunting of fibers into wrong channels with the former method. When the nerve is crushed a second time, sixteen to forty-two days after the initial injury, recovery occurs earlier than after a single crush, a fact which may be attributed to a surplus of Schwann cells produced by the second interruption. 3. Interference with the blood supply to the limb. This does not delay the recovery of the muscle. 4. Cross union, such as that between the central stump of the tibial nerve and the peripheral stump of the peroneal nerve, leads to limited recovery of function. This does not imply central relearning, since the tibial nerve contains some fibers which innervate muscles normally producing spread of the toes. 5. Delayed suture. This tends to retard recovery, but the effect is pronounced only when the delay exceeds six months. 6. Infection. The effects vary from delayed recovery to no appreciable influence. 7. Age. Recovery tends to be more speedy in young animals than in old ones.

MALAMUD, Ann Arbor, Mich.

PROCAINE NERVE BLOCK IN THE INVESTIGATION OF PERIPHERAL NERVE INJURIES. W. BREMNER HIGHET, J. Neurol. & Psychiat. **5**: 101 (July-Oct.) 1942.

According to Highet, peripheral nerve block affords a useful method of investigating the function of peripheral nerves. The technic employed by the author consists of injection of a 2 per cent solution of procaine containing epinephrine in a concentration of 1 : 50,000 and the use of an apparatus designed for direct unipolar stimulation of the nerve into which the solution is injected. The criteria of completeness of the nerve block thus produced are: (*a*) full vasodilatation, anhidrosis, anesthesia and analgesia in the autonomous zone of the nerve and (*b*) complete and lasting paralysis of muscles supplied by the nerve distal to the site of the block. The method has been useful in investigation of the following problems: 1. Anomalous innervation of muscles. 2. "Supplementary" and "trick" movements. The former are performed at a joint by the contraction of muscles which are able to take over the function of the paralyzed muscles. These movements are to be distinguished from true trick movements, which are passive and are brought about by tension on paralyzed muscles due to the over-action of their antagonists, by "rebound" or by the action of gravity. 3. Sensory and sudomotor distribution of peripheral nerves. One must take into account factors due to nerve overlap, such as the difference in extent between the autonomous and the maximal zone of sensory distribution and the initial progressive shrinkage of the area of sensory loss following nerve section before actual regeneration has set in. In this way one can distinguish complete from partial and recovering lesions of peripheral nerves. 4. The vasomotor distribution of peripheral nerves. The author is of the opinion that this is identical with the distribution of unmyelinated fibers subserving sweat and pain functions. In some cases of causalgia sympathetic nerve block is useful before sympathectomy is performed.   MALAMUD, Ann Arbor, Mich.

FACTORS AFFECTING RECOVERY OF SENSORY FUNCTION AFTER NERVE LESIONS. E. GUTMANN and L. GUTTMANN, J. Neurol. & Psychiat. 5:117 (July-Oct.) 1942.

In order to study recovery of analgesic areas after lesions of nerves, Gutmann and Guttmann first mapped out the maximal and autonomous zones of the cutaneous distribution of the peroneal, tibial, sural and posterolateral cutaneous nerves of the thigh and the saphenous major in the rabbit. They found that recovery of sensation after denervation may be divided into three phases: 1. Recovery in zones of overlap by the progressive resumption of function by fibers of adjacent nerves. These zones are formed where several nerves meet, the pattern depending on the anatomic supply of the subject's peripheral nerves. Pure cutaneous nerves, such as the sural, internal saphenous and lateral cutaneous, show extensive overlap on both the proximal and the distal border, whereas with mixed nerves, such as the tibial and peroneal, the overlap on the distal distribution is negligible. Recovery in zones of overlap generally occurs two to four weeks after interruption of the nerve, but in young animals it may take place after a few days. Recovery is susceptible to various factors, such as local damage of the skin supplied by adjacent nerves, transient block of these nerves as a result of operation and all processes which tend to raise nerve thresholds, such as infection, narcosis and age. 2. Recovery by local extension of fibers into the autonomous zone. This plays a role when a small analgesic area is surrounded by other nerves, but not in recovery of sensation in larger areas or with mixed nerves. 3. Recovery in the autonomous zone of a nerve by true regeneration. This proceeds in a downward direction, the recovery advancing faster at the edges than in the center, so that the analgesic area shrinks concentrically. The process is the same after a lesion of any nerve. The margin of algesia makes a general advance, so that estimation of the rate of recovery is permitted. This rate is affected by various factors, chiefly the nature of the lesion. Thus, after suture the recovery is slower than after crushing of the nerve, the rate for the latter being 3.35 mm. per day and the latent period of twenty-two days, as compared with 2.46 mm. per day and a latent period of forty days with suturing. The peripheral delay apparently depends on the arrival of new fibers and their maturation. The rate of advance of algesia is faster when the nerve is crushed at the ankle than in the thigh. Crushing the nerve over a stretch of 4 cm. delays recovery by two weeks. The greater success following crushing is apparently due to the fact that the Schwann sheaths maintain their continuity.

MALAMUD, Ann Arbor, Mich.

PARALYSIS OF LEFT RECURRENT LARYNGEAL NERVE FOLLOWING SUBCUTANEOUS ADMINISTRATION OF ANTITETANIC SERUM. H. S. FLOYD, W. E. PEMBLETON and P. P. VINSON, West Virginia M. J. 38:253 (July) 1942.

Floyd and his co-workers report what they believe to be the seventh case of paralysis of the left recurrent laryngeal nerve and of both brachial plexuses following subcutaneous prophylactic administration of 1,500 U. S. P. units of tetanus antitoxin. The patient gradually improved, and within three and a half months the function of the arms was normal. The voice gradually returned to normal, and within six months of onset the larynx appeared normal on inspection.

J. A. M. A.

INNERVATION AND FUNCTION OF THE THENAR MUSCLES. W. BREMNER HIGHET, Lancet 1:227 (Feb. 20) 1943.

Highet cites several cases of complete division of the median nerve in which a faulty diagnosis of an incomplete or a recovering lesion was made because of good action in one or the other of the thenar muscles, which classically are innervated by the median nerve. The muscle giving rise to the greatest difficulty is the flexor pollicis brevis. Stopford stated that "the flexor pollicis brevis is composed of several slips, some supplied by the median, others by the ulnar, which are subject to considerable variation."

In a case of injury to the median nerve in which some activity is preserved in one or the other of the thenar muscles, there must be some means of deciding whether the innervation of the thenar muscles is anomalous or whether the injury to the nerve is incomplete. There are two methods of investigation: First, bipolar percutaneous faradic stimulation of the ulnar nerve just above the pisiform bone may produce a response in all intrinsic muscles of ulnar innervation. Second, a peripheral nerve block may be made. Procaine with epinephrine is injected percutaneously in or around the nerve to be tested. If the technic is satisfactory, all conduction in the nerve tested may be abolished for two to four hours. The nerve block may be performed in one of two ways: Either the injured median nerve may be blocked immediately above or below the site of injury, or, better, the nerve believed to be responsible

for the anomalous innervation of the thenar muscles is blocked. In all the cases cited by Highet this has been the ulnar nerve. A favored site of ulnar nerve block is at the level of the medial epicondyle.

Twenty cases of complete division of the median nerve are cited, with a detailed examination of the thenar muscles, both before and immediately after suture of the nerve. In this series the flexor pollicis brevis was shown to be innervated by the ulnar nerve in 16 cases (80 per cent). In 4 cases there was some action of the opponens pollicis, in addition to the flexor pollicis brevis. In 2 cases there was also some action of the abductor pollicis brevis after injury to the median nerve.

Of 25 cases of proved division of the ulnar nerve, obvious wasting of the flexor pollicis brevis was evident in only 1 case. The absence of obvious wasting and paralysis is not surprising, since the flexor brevis usually receives its innervation from both the median and the ulnar nerve. In cases of division of the median nerve the activity of the muscle is due to the preservation of its ulnar innervation and is readily noted because of the paralysis and wasting of the abductor pollicis brevis and the opponens pollicis. In cases of division of the ulnar nerve the muscle is still active because of its median innervation, wasting being obscured by the overlying abductor pollicis brevis.   SANDERS, Philadelphia.

NEURITIDES ACCOMPANYING SYPHILITIC AORTITIS. A. BERNER, Confinia neurol. **5**:13, 1942.

Berner expresses the belief that in most instances the nerves supplying and contiguous to the aorta are affected by the disease process in syphilitic aortitis. The changes observed were those of neuritis and perineuritis. Of the 15 cases studied the recurrent nerve was involved in the neighboring inflammation of the aorta in 8 and the vagus nerve in 3. Inflammatory changes in the sympathetic ganglia were often noted. The author attempts to differentiate between the nervous phenomena resulting from compression associated with dilatation of the aorta and those definitely associated with inflammatory changes in the nerves themselves.

DeJong, Ann Arbor, Mich.

POLYNEURITIS FOLLOWING THERAPY WITH A SULFONAMIDE COMPOUND. ADHERBAL TOLOSA and CARLOS V. SAVOY, São Paulo med. **12**:269, 1939.

Tolosa and Savoy discuss the sulfonamide compounds, their uses and contraindications, and relate a case of acute gonorrhea treated with alchysulfamide (uliron). A total of 40 Gm. was given a youth aged 18 in thirteen days. About a week after cessation of the treatment the patient began to lose strength in his legs and to walk unsteadily and soon was bedridden. He had the signs of polyneuritis with tenderness of the calves, muscular weakness and absence of the achilles reflex. He was given injections of strychnine and vitamin B_1, massage and galvanotherapy. After five months he began to improve slowly. The authors note other cases of polyneuritis provoked by this drug which have been reported in the medical literature.

BAILEY, Chicago.

Society Transactions

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

WILLIAM G. LENNOX, M.D., *Presiding*

Regular Meeting, April 15, 1943

Psychiatry in an Army General Hospital. LIEUTENANT COLONEL DUNCAN WHITEHEAD, Medical Corps, Army of the United States.

A Psychodynamic Study of a Group of Patients Suffering from Arterial Hypertension. DR. CARL BINGER.

This paper is an abstract of a study made by Dr. N. W. Ackerman and myself, in collaboration with Dr. A. E. Cohn, Dr. H. A. Schroeder and Dr. J. M. Steele, of the staff of the Hospital of the Rockefeller Institute for Medical Research. The work was aided by a grant from the Josiah Macy Jr. Foundation. It will appear as a monograph, to be published by *Psychosomatic Medicine*. The personality studies were conducted by Dr. Ackerman and myself; the clinical studies, by our associates.

An effort was made to understand the life histories of 24 patients suffering from arterial hypertension in terms of motivation: to trace, in each instance, the character development, the time of onset of neurotic traits and the appearance of prodromal symptoms and of hypertension and to discover the interrelations of these events. In this paper only 1 such history is given in any detail—that of a young woman whose early childhood was threatened by great insecurity, due chiefly to her father's violent nature. The effect of this early environmental situation was worked out in relation to her whole subsequent emotional growth, and the meaning of violence to this patient was explored, with particular reference to an event of traumatic significance which was associated with the onset of her hypertension.

The existence of such traumatic situations and the emotional responses to them were described for this patient and for the others. In 23 of the 24 patients hypertension was discovered shortly after such an emotional disturbance. The failure of the integrative functions of the personality, the inefficiency of the repressive mechanisms and the inability to form organized neuroses, rather than the nature of the underlying drives, are what appear to differentiate this personality disorder from other seemingly similar ones.

Evidences of this peculiar personality are discernible before hypertension or its prodromal symptoms supervene. It may be concluded, therefore, that the "neurotic" manifestations are not the result of high blood pressure itself.

DISCUSSION

DR. STANLEY COBB: First, we of this society welcome Dr. Binger home; he spent about ten of his formative years here, and we are proud of him.

As to the work itself, he has presented many interesting observations, which were well and meticulously made. A great deal of work is needed in examining these patients and in learning about them so intimately. It is hard to make an exposition of the results in half an hour, and Dr. Binger is to be commended on presenting one excellent case and then mentioning the others. All, I suppose, would accept the mechanism of autonomic mediation of the emotions and expression of the emotions. The idea behind it all originated with Dr. Walter Cannon, who showed the effect of the emotions; we have learned about and observed such expressions in human beings. Many clinical syndromes are seen; when one of them *is* described as being related to a certain personality type, I become skeptical.

Among the main symptoms Dr. Binger mentions are loss of love of parents, anxiety and suppression of hate, submissiveness, suppression of warmth, stubbornness, recklessness, amnesia, lack of emotional ability to express oneself and avoidance of sex. From my own experience, I should say that these symptoms are remarkably like those I have observed in persons with Raynaud's disease. About half of them appear in persons who have arthritis; the others are rare with arthritis. They are quite unlike the personality traits seen with eczema. Persons who react with symptoms referable to the heart and circulation present about half these symptoms. That is a rough summary of experience. Does it mean that we physicians should work harder along psychologic lines, or are we barking up the wrong tree? I think we should

look up the family tree. No study of inheritance and individual susceptibility to system neurosis has been made. I believe there is a great deal in the old Adlerian idea that one inherits a weakness of one or more systems and that as one is burdened with stress that system is affected.

I was especially interested in Dr. Binger's demonstration that hypertension presents a special situation in that the symptoms are not episodic, since in all patients I have worked with they were episodic. Such patients are easier to work with because one can associate an episode with an emotional situation. I should like to ask why anxiety in one person causes renal ischemia, while in another it may produce hyperemia of the stomach, as observed by Wolff, and in another rectal hyperemia. Some women stop menstruating, and others have excessive menstruation, after a period of anxiety.

Dr. REGINALD H. SOUTHWICK: (Slides were shown illustrating the pathologic physiology of the hypertensive state and the effect of surgical intervention on the vasoconstrictor pathways to the visceral vascular bed.)

Dr. ROBERT S. PALMER: I appreciate hearing Dr. Binger's paper. I have been interested in the medical care of hypertensive patients and have been associated with Dr. Smithwick's work. I cannot pretend that my psychologic reviews would pass muster here. However, my associates and I have made the best psychiatric study possible of our patients. The outstanding finding is that the patient is insecure and seems to have an unusual need for success. Actually, in my experience the patients frequently have been very successful and well integrated. There is no doubt that nervous factors cause episodic increases in the blood pressure and that the level of the blood pressure and the general well-being vary directly with the general life situation. Nevertheless, hypertension, once fully established, rarely regresses to normal with psychotherapy. There are exceptions. Transient nervous hypertension in young adults, better called potential hypertension, apparently does regress, either spontaneously or with lessening of the anxiety.

It is hard to get control material except from patients without vascular disease, but I have the impression that most patients with hypertension are well organized. Perhaps the strain of integration contributes to the progress of their disease. When hypertension is discovered, there is normal concern on the part of the patient. It is hard to say at what point normal concern becomes abnormal anxiety. Certainly, when anxiety is minimal or, as in some instances, absent, the so-called hypertensive symptoms are absent. Nevertheless, when the symptom anxiety (with its physical concomitants) is relieved, the level of the blood pressure as a rule remains abnormally elevated.

In short, anxiety about the blood pressure, not the level of the blood pressure, is the precipitating cause of the symptoms in the majority of patients with mild and moderate degrees of hypertension. In my opinion, anxiety concerning the blood pressure may be a factor in the progress of the condition. This, of course, is not true in the late stage of the disease or in malignant hypertension, when either thrombosis or vascular spasm results in actual circulatory insufficiency in the brain.

Dr. IVES HENDRICK: I especially enjoyed the paper from the point of view which Dr. Cobb suggested, namely, that it is a contribution not only to the study of hypertension but to the more general problems of psychosomatic disease. It is important to recognize as clearly as Dr. Binger does that one is really studying the physiologic process by two distinct methods— the laboratory and the psychologic. It is not a question of whether Goldblatt's studies of ischemia of the kidneys are relevant or of whether the psychoanalytic approach to the treatment of hypertension is relevant. Rather, there are two separate and supplementary methods of studying essentially the same problem. The psychologic approach gives a picture of what has happened emotionally, and therefore of what is happening to the autonomic nervous system as a whole; the study of the autonomic nervous system by the laboratory method is a more direct and precise approach to investigation of the organs but reveals less of the interrelations of the total organism. The author's illustrative case has shown that emotionally traumatic experience plays an important role in precipitating hypertension. It illustrates certain experiences to which a person cannot respond adequately and are therefore traumatic because they lead to a breakdown at the weak point in his physiologic equipment. What differentiates the point of breakdown in a person in whom hypertension develops from that in one in whom, say, a gastric ulcer forms, is a larger problem. How much the family history will show is a question that cannot be answered tonight. But it is reasonable to assume that a person cannot break down in a certain system unless he has some potentiality to do so. This does not mean, however, that the predisposition is entirely hereditary, that weakness of a particular system may not be due to certain experiences of infancy that are hard to investigate.

I should like briefly to compare the persons with psychosomatic disease with those who have a psychoneurosis. Dr. Binger's comment that hypertensive persons do not seem capable of organizing psychoneurotic symptoms is extremely relevant from the psychoanalytic standpoint. As Dr. Smithwick pointed out, the particular personality traits of this group do not seem to be unique in, or peculiar to, hypertensive persons. Amnesia for childhood experiences and inability to express oneself adequately, especially the inability to express one's aggression, and the fear of even feeling aggressive lead to an outward dependency and the appearance of good adjustment so long as the person can avoid situations which are acutely disturbing. This excellent relation to the environment, together with a low threshold of emotional tolerance, seems to be characteristic of hypertensive persons and of those with many of the other types of psychosomatic disease which Dr. Cobb has mentioned, such as gastric neuroses.

I should, also, like to mention that the constitutional factor of a tendency to react with instability of the neurocirculatory system is not limited to those who manifest psychosomatic symptoms. One sees it in patients with anxiety hysteria who blush easily or exhibit more frank anxiety symptoms. Patients with psychosomatic disorders do not commonly have such disease early in life, but they do have some organization of a psychologic symptom which relieves the tendency—for example, a phobia. In my opinion, it is frequently true that people who seem unusually well organized are those who are insufficiently adaptable to strain to discharge their tensions in a psychoneurotic way. From this standpoint, psychoneurosis may well be considered a blessing, a sort of safety valve which enables the person to suffer without breakdown of an organ system.

One patient had a severe psychoneurosis and died suddenly of cardiac failure. In early puberty he was considerably upset and then became extremely well organized and adjusted until he went to college. For the first two years of college he went "haywire." He was disciplined by his parents, the authorities and his fraternity brothers. Then he became particularly well organized. He had a brilliant career but eventually suffered a sad breakdown. That case brought home to me the misfortune of premature ability to deal so effectively with one's problems that they are never really solved until one pays the price with a psychosomatic breakdown, which may lead to death.

Dr. Isador H. Coriat: My own analytic experience with these disorders has led me to a different angle of interpretation. My feeling is that these patients had at the beginning a severe character disorder or were essentially of a neurotic type. Behind the hypertension in all these patients one can, I believe, find certain specific reactions, such as hate, stubbornness, aggression or hostility. In other words, the total personality of the patient must be taken into consideration, not only the specific life situation which precipitated the hypertension or some other psychosomatic syndrome but the particular development of his personality from childhood up; then I think that one will be able to correlate a neurosis, an asthmatic disorder or a high blood pressure level with specific dynamic trends, either conscious or unconscious. In analytic work these trends are primarily unconscious, and they affect either the particular organ of which the patient complains or produce a form of hypertension.

Dr. Carl Binger: With reference to Dr. Cobb's comments, the first point at issue is one of semantics. When I said "peculiar," I meant "peculiar," not "unique." These character traits are peculiar to hypertension. They may also be peculiar to other diseases. I did not mean to imply that they were unique, nor did I intend to make a phrenologic list of neurotic character traits and say, "This is hypertension." I tried to present one life history and to show how events in the patient's childhood and subsequent events of later life led up to a certain *denouement,* which physiologically is recognized as hypertension and psychologically as a kind of decompensatory process.

Dr. Hendrick's comment seems to me much to the point. To understand so complicated a problem as hypertension, one needs to look at it both physiologically and psychologically.

Dr. Smithwick's work has been of interest to me for a long time. What the operation does in the psychologic sphere I do not know. It has proved significant to some of these patients. Certainly, many of them have shown extraordinary improvement not only in the level of the blood pressure but in their whole outlook.

In regard to Dr. Palmer's observations, I should use not the word "integration" but the word "suppression." By struggling these patients succeed in keeping down impulses which cause them a great deal of difficulty. One of the significant things about them is their incapacity for development of sustained organized neuroses. They have fleeting episodes in the form of neurotic symptoms. Perhaps, if they could sustain such symptoms, their blood vessels would be spared. This, of course, is speculation.

PHILADELPHIA NEUROLOGICAL SOCIETY

GEORGE D. GAMMON, M.D., *Presiding*

Regular Meeting, April 23, 1943

Familial Periodic Paralysis. DR. ALEXANDER SILVERSTEIN.

Familial periodic paralysis is a rare disease characterized by recurrent attacks of flaccid paralysis, associated with diminution or loss of the deep reflexes and inexcitability of the muscles to electrical stimulation. Many theories have been advanced to explain these paroxysmal transient seizures. Until recently practically no treatment was known to prevent or influence the attacks.

Since 1937, when Harrington reported on the beneficial effect of potassium citrate in the treatment of this condition, interest has been greatly stimulated. Pudenz and his group, in Montreal, Canada, and Gammon and his collaborators, in Philadelphia, as well as other investigators, have published important observations on the chemical aspect of the disease. These investigators found that attacks of paralysis are associated with a pronounced fall of potassium in the serum and that the administration of an adequate amount of potassium salts brings about rapid recovery. Prompt improvement is also effected by the introduction of carbaminoylcholine chloride and mecholyl chloride into the blood stream (Pudenz, R. H.; McIntosh, J. F., and McEachern, D.: Role of Potassium in Familial Periodic Paralysis, *J. A. M. A.* **111**:2253 [Dec. 17] 1938). Attacks have been produced by the administration of dextrose, epinephrine and ephedrine and by water diuresis.

That familial periodic paralysis seems to be an inborn error of metabolism is provocative and should stimulate work on other hereditary diseases of the neuromuscular system which at present are looked on with pessimism.

REPORT OF A CASE

A boy aged 9 years was admitted to the Philadelphia Hospital for Contagious Diseases with a condition diagnosed as acute anterior poliomyelitis. The history of the onset was that of rapidly developing ascending paralysis. When the boy was examined several hours after the onset there were complete flaccid paralysis of both lower extremities and marked weakness of the upper limbs, including the group of shoulder muscles. The deep reflexes were greatly diminished. The patient was not acutely ill; the sensorium was unaffected, and he did not complain of any soreness or pain in the muscles; there was no increased tension of the muscles of the neck or any sign of spinal involvement. The spinal fluid was not under increased pressure and showed no increase in cells. The results of all studies were within normal limits. There was no elevation of temperature or change in pulse rate. The morning after admission the patient was sitting up in bed, apparently well. Examination disclosed complete absence of all signs of paralysis. The dramatic recovery was so striking that several observers considered the diagnosis of hysteria. When the boy was questioned, it was learned that he had had a similar episode previously. I did not see the patient until three years later. A few days prior to the present admission he had a severe attack, which began early in the morning (about 4 a. m.) and persisted until the next evening. The attack consisted of complete paralysis from the toes to the neck. He was unable to open his mouth; his head "flopped" in all directions; he had great difficulty in breathing; in fact, the family thought he was dying. The patient informed me that since his discharge from the hospital he had had numerous attacks of sudden paralysis of the extremities, sometimes several a week. Invariably they occurred in the early hours of the morning, often awakening the patient from sleep. Occasionally the paralysis affected only one extremity, usually the arm. The attacks came on suddenly, without warning. Seasonal variations, especially spring and summer, gave rise to a striking increase in the frequency and severity of the attacks.

The patient is the youngest of 7 children. Five of the siblings are said to be well. The mother and her oldest child also suffered from the same attacks as the patient. The mother's paralytic attacks commenced at the age of 15 years. They occurred early in the morning and consisted of loss of power in the arms and legs, lasting about two or three hours and recurring about once every two or three months. The attacks had become much more frequent, occurring about three or four times a week and increasing in severity during the period of gestation of the youngest child (my patient). Since the age of 35 she had had no further attacks. The oldest child was stricken with infantile paralysis at the age of 18 months; this illness left him with deformity of a limb. He began to have the attacks of paralysis at 14 years of age and is said to have had about three such attacks a year. He died during a severe attack, at the age of 16. According to the mother's description, the attack began early in the morning, and within a short time he was unable to move any part

of his body from the neck down. He could hear, see, talk and swallow, and his mind was said to have been perfectly normal. Death occurred within twelve hours.

General Examination.—The boy was moderately obese, the adiposity being chiefly of the girdle type. The heart and lungs were normal. The blood pressure was 120 systolic and 70 diastolic. The disks were not choked. The pupils reacted to light and in accommodation. The significant changes were the unusual hypotonia and the alterations in the muscles, changes strongly suggesting dystrophy. The truncal and the gluteal muscles were chiefly affected. On arising from a reclining position the patient used the method of "climbing" up on his thighs so frequently seen in cases of muscular dystrophy. He was given potassium citrate, 30 grains (1.95 Gm.), three times a day for three weeks, with definite improvement in that the attacks were mild, although just as frequent. From Sept. 25, 1943 until the present time the patient has been receiving potassium chloride, 7 to 12 Gm. a day. It was found that large doses during the day would not prevent an attack the following morning. At present the patient is taking 4 Gm. at 8 a. m. and 4 p. m. and 16 Gm. at 2:30 a. m. It was noticed that during March 1943, with the frequent changes in the weather, the attacks became more frequent, and the dose had to be increased. At the beginning of an attack the patient takes 4 to 8 Gm. of potassium chloride, and improvement is noted within fifteen minutes and complete disappearance of symptoms in about two or three hours.

Comment.—I believe the clinical picture in this case is fairly typical of familial periodic paralysis, as recorded in the literature. The resemblance of periodic paralysis to anterior poliomyelitis and Landry's paralysis should be borne in mind. It should also be noted that the condition can readily be confused with hysteria, especially in sporadic cases. Periodic paralysis has been recognized as a clinical entity since 1882. The hereditary nature of the condition is evident in about 80 per cent of all cases which have been reported. The disease may be transmitted either as a dominant or as a recessive character. Sporadic cases have been described.

The condition usually makes its appearance in the first or second decade of life. The attacks have a tendency to diminish in frequency and intensity during middle life and to disappear in later adult life. The mother of my patient ceased to have attacks after the age of 35 years. Exciting factors are claimed to be strenuous exercise and intake of large amounts of carbohydrates. Most of the reported cases indicate a predilection for the male sex, the ratio of the sexes being 3:1. The disease varies in different families with respect to the mode of transmission, the time of onset, the severity and frequency of the attack and the prognosis, but the pattern of the attack seems to be more or less constant for the stricken members of the family. The attacks are more common during the night and early morning and seem to be precipitated by the patient's remaining quietly in one position for a prolonged period. Paralysis of the flaccid motor type may affect all the voluntary muscles except the face, mouth, throat and sphincter. Although death rarely occurs, in serious cases the muscles of respiration and deglutition and the muscles of the neck become involved, and death may follow. This fatal outcome occurred in the case of the patient's brother, and the patient himself had a severe attack during which he almost died. Some authors have stressed the relation of periodic paralysis to other familial diseases, such as migraine, epilepsy and hereditary myopathies. Of particular interest is the combination of periodic paralysis and dystrophy, as reported by several authors. My patient also shows signs of early dystrophy, affecting chiefly the proximal portions of the limbs and the truncal and gluteal muscle groups.

DISCUSSION

Dr. J. W. McConnell: I have nothing to add to this presentation except to say that it recalled to my mind a case occurring some years ago, when Dr. Spiller was holding clinics at the University of Pennsylvania. A boy was brought into the clinic paralyzed in all four extremities, with loss of all reflexes. Dr. Spiller examined him closely and said he must have acute anterior poliomyelitis. The next morning the boy was practically recovered. One of the assistants in the clinic, Dr. W. B. Cadwalader, suggested that the case might be one of familial periodic paralysis. Spiller disagreed because of the absence of other cases in the family, but Cadwalader said, "But, it has to start with somebody."

Lieutenant (sg) Axel Olsen, U. S. N. R.: Dr. McConnell says that family history must start somewhere. In 1936 I saw a man with a history of illness almost like the one just reported. His family history was perfectly clear. His muscles also were weak but appeared well developed; from his appearance one would think he should have the strength of a giant, but between his periods of acute paralysis he was as weak as a child. During the attacks of paralysis he lay completely flaccid, with electrical reactions diminishing to the vanishing point. Biopsy of muscle showed patches of disrupted fibers. The pathologist did not want to name what he saw, stating that the condition of the muscle was abnormal

but that he could not explain why. It was not the muscle of progressive muscular dystrophy. I wonder what a biopsy of this patient's muscle would show.

DR. GEORGE D. GAMMON: It might be interesting to say a word about the history of potassium therapy of this disease. In 1905 Dr. G. E. Holtzapple used potassium bromide in treatment of this condition, although at the time it was not known to him that potassium was the effective agent of relief. This remarkable practitioner of medicine, in York, Pa., discussed with his friend, Dr. William Osler, the possibility of presenting before the state medical society a family members of which suffered from periodic paralysis. Dr. Osler made the diagnosis of "family periodic paralysis" and asked Holtzapple to record the number of cases, which was the largest occurring in a single family reported in the literature.

Because migraine was associated with their condition and because migraine was attributed to vascular spasm, and the antispasmodic of the day was bromide, Holtzapple gave the members of the family potassium bromide in increasing doses until the attacks were relieved. In the editions of Osler's textbook of that period bromide is listed as a specific remedy for this condition. In subsequent editions it was dropped, because other physicians had used sodium bromide and did not obtain relief.

My first contact with this condition was made while I was studying the effect of prostigmine on myasthenia. I read a paper on that subject and Dr. W. S. McCann, of Rochester, Minn., commented that he had a patient with familial periodic paralysis who was a descendant of the family reported on by Mitchell in whom potassium citrate had aborted an attack. Mitchell recorded abortion of the paralysis, slowly, within twelve hours after administration of potassium citrate. This clue was dropped by Osler after Holtzapple had reported the effect of bromide. Earlier editions of Osler's textbook had recommended the use of potassium citrate, as proposed by Mitchell, Pemberton and Edsall. Later, Harrington stated that he was able to abort an attack with potassium citrate, but not to abolish one.

About this time I treated a man with familial periodic paralysis with large doses of potassium chloride, with immediate and dramatic improvement. With Dr. Austin and others, I then studied the serum and found a low potassium content. In England, Allen and associates had previously recorded a low potassium level in the serum and had found that potassium chloride would relieve an attack. About this time a good deal of work was reported on the relation to the disease of the potassium in the blood; these studies showed that the potassium content was lowered during a seizure and that there was no previous excessive urinary excretion of potassium during the attack.

For about four years I have treated with potassium a patient with daily attacks, and he has been able to get along fairly well by taking a dose in the early morning hours. There has been some regression of the testicles during that period, but otherwise he has been well. In this patient, inactivity undoubtedly brings on attacks. He can sit down for an hour and become weak. Characteristically, the inactivity of sleep is associated with the onset. There is a dramatic case in the literature in which a man was copying music at a desk and became paralyzed in all extremities except the one with which he was writing. Electrical stimulation of a muscle will improve its function providing the patient is not completely paralyzed at the time. Have any studies been made on the potassium content of the serum in this boy?

The potassium level can be lowered by administration of epinephrine. It appears that the weakness in these patients is due to something else. All my studies have led to the conclusion that something happens to the muscle itself, and it seemed possible that the correction of this muscular defect drew potassium out of the serum. My colleagues and I based our opinion on the abnormality of the muscle itself, in view of the fact that the electromyogram was distorted. That is an experimental observation, which may not be accepted by all investigators.

DR. A. M. ORNSTEEN: Dr. Gammon, would you draw any comparison between this disease and myasthenia gravis, the only difference being in the clinical periodicity of the paralysis?

DR. GEORGE D. GAMMON: The two diseases are almost exact opposites. Activity makes myasthenia worse and improves familial paralysis. Myasthenia is like a curarization block; the muscle itself is normal, and although potassium will help myasthenia, it will not relieve it to the degree that it does familial paralysis. The effect of prostigmine on myasthenia is comparable to the effect of potassium on familial paralysis. The studies show that myasthenia is like curarization, whereas familial paralysis appears to be a muscular defect.

Acute Ascending Paralysis; Landry's Paralysis. LIEUTENANT (sg) AXEL OLSEN, U. S. N. R.

As is well known, the group of diseases characterized by acute, rapidly ascending paralysis with minimal sensory changes has been designated by many terms. Perhaps the earliest and best known name is Landry's paralysis. It is recognized that this term is only one

applied to designate a symptom complex. The following 3 cases may not fit every neurologist's conception of Landry's syndrome, but they were felt to be sufficiently interesting to justify report, since all the patients were seen within eighteen months, all recovered and no apparent etiologic agent was discovered in the case of any of them.

REPORT OF CASES

CASE 1.—S. J. U., a white man aged 25, was admitted to the hospital on June 23, 1941, with the chief complaint of diffuse pain throughout the right leg, the pain being much worse at night. This had been preceded by three weeks of "limping with the right leg." The patient stated he did not know why he had limped, since he had had no pain in the extremity at that time. There was no complaint of numbness in either extremity. Physical examination revealed nothing abnormal except slight enlargement of the prostate and mild bilateral antritis. Neurologic examination showed slight weakness of dorsal and plantar flexion of the foot, decrease in the knee jerk and absence of the ankle jerk on the right side. Tenderness along the course of the sciatic nerve and a positive Lasègue sign were noted on the same side. The family and personal histories were not contributory except for an attack of gonorrheal urethritis three months before. The results of urinalysis, a blood count and serologic studies of the blood were normal, as was the sedimentation rate. A submucous resection was done to help eradicate the foci in the antrums, but the complaints persisted, and on July 7 the pain was extreme, being located chiefly in the right hip. The knee jerk had disappeared, and he had an obvious foot drop on the right side. The next day lumbar puncture revealed extremely xanthochromic fluid, which contained 400 mg. of protein per hundred cubic centimeters and 38 cells, of undescribed type, per cubic millimeter. By this time he complained of a twitching sensation in the muscles of his left leg. Four days later the ankle jerk was observed to be absent on the left side; the knee jerk was diminished, and weakness of the calf and the anterior tibial muscles of the left leg was obvious. The right leg was barely capable of motion. Another lumbar puncture showed a subarachnoid block; so a study with iodized poppyseed oil was carried out, revealing an obstruction at the first lumbar vertebra. Two days later (twenty days after the onset of pain) urinary retention developed. Sensory examination still gave normal results, and the white blood cells numbered 14,500. Because of the apparent block a laminectomy was done on July 16, 1941; it revealed an area of swelling in the cord, measuring 2 cm., and localized arachnoiditis at the level of the twelfth thoracic vertebra. During the week after operation the paralysis of the legs became complete, and slight hypesthesia, of diffuse type, developed in the legs, with no definite level of sensory loss. Two weeks after operation paralysis of the third nerve developed bilaterally, with dilated pupils and ptosis, and cisternal puncture revealed elevated pressure and blood-tinged fluid. The patient continued in this condition for another month; he became emaciated; a decubitus ulcer developed, and his mental attitude approached that of acute mania. On August 31, six weeks after operation, and after repeated lumbar and cisternal punctures, roentgen irradiations and vitamin therapy, it was noticed that he had a little movement in both feet, and a week later he began to void spontaneously. From then progress was steady, and he was discharged on April 2, 1942, to return to duty, with only absence of the ankle jerk and decrease in the knee jerk on the right side and very slight weakness of both flexion and extension of the right foot. He was seen again on Aug. 15, 1942, at which time his condition was unchanged.

CASE 2.—This case undoubtedly is a more typical instance of Landry's syndrome than the first case. E. F., a white man aged 50, was admitted to the hospital on April 22, 1942. His presenting complaint was prickling in the hands and feet for three days and weakness of the knees for two days. No other complaints were noted. The family history was without significance. He gave a history of a fairly severe cold, lasting one week, which disappeared a month before the present illness, and excessive alcoholism for three years, from which he recovered in 1940. He was employed in a paint-spraying establishment and worked with an unknown solvent. Physical examination showed mild arteriosclerotic changes but no other gross abnormality. Neurologic examination revealed complete areflexia, paralysis of the legs, tenderness on compression of the calves and decrease of vibration sense in the ankles. The cranial nerves were intact. The results of laboratory studies, including lumbar puncture, were normal in all respects, the spinal fluid showing 2 cells per cubic millimeter and a total protein content of 30 mg. per hundred cubic centimeters. The serologic reactions were negative, and the electroencephalograms showed no abnormality. Three days after admission the paralysis had involved his arms, and he was having difficulty in breathing. Signs of pneumonia were developing, and fluoroscopic examination of his chest revealed paralysis of the left side of the diaphragm; so treatment with sulfathiazole was started. Six days after admission no motion was present in either arm or leg, and the sensorium and cranial nerves were still intact. Two days after this he noticed a little movement in his arms, being able to

raise them three or four inches (7.5 or 10 cm.) from the bed. Five days later (two weeks after admission) urinary retention developed and catheterization was necessary. The pneumonic process was growing worse at this point, and administration of oxygen was begun. Erythematous dermatitis developed on his hands and face, becoming much more severe after five days. By that time the condition in his chest was improving, so that the sulfathiazole therapy was stopped; the dermatitis improved immediately, and his general status showed slow but steady improvement. On May 16, three and a half weeks after admission, motion was present in all joints except the ankles. He had slight hypesthesia of the lower portions of the legs, and vibration sense was absent in the ankles and wrists but was present, though decreased, elsewhere. The reflexes were still absent. Lumbar puncture on May 18 showed a protein content of 35 mg. per hundred cubic centimeters of spinal fluid. On June 11 he could walk with assistance, and on June 25 he was discharged, the reflexes being normal, the strength good and sensation normal throughout. His calves were still slightly tender, but the nerve trunks were normal on palpation.

CASE 3.—J. H. S., a white youth aged 18, was admitted to the hospital on Feb. 26, 1943. His presenting complaints were weakness of the knees, which he had first noticed three days before, while marching, and weakness of the left shoulder, which developed on the way to the hospital, in the ambulance. He had also noted a little pain in the left shoulder, some soreness of the calves and slight prickling and tingling in the toes. The family history was without significance. Two weeks before, he had had an infection of the upper respiratory tract, of three days' duration. He had noticed occasional pain in the left shoulder for the past year and acute pain in the shoulder during September 1942. Neurologic examination showed the absence of reflexes in the legs, the absence of abdominal reflexes, the presence of cremasteric reflexes and barely obtainable biceps and triceps reflexes. Sensation was normal throughout. He walked with a wide base, with the abdomen protruded, the arms swinging loosely and the knees lifted high. There were almost complete paralysis of the lower part of the left leg and pronounced weakness of the right leg. The flexors of the thigh and knee were weak, but the strength of the extensors was fair. The muscles of the abdomen were weak, as were those of the lumbar portion of the spine, but movements of the thorax and those of the diaphragm were good. There was extreme weakness of all the muscles of the right arm and of those of the left arm except the deltoid, which was paralyzed. The muscles of the neck and the cranial nerves were normal. No fibrillations were noticed, and there was no atrophy. Laboratory studies gave normal results except for a white blood cell count of 15,700. The differential count was normal, and lumbar puncture revealed normal spinal fluid. Rest in bed was the only treatment initiated; two days later his condition was definitely improved, and in a week he was up and about, only slight weakness of the left shoulder remaining. Improvement was most rapid in the legs. On March 15, seventeen days after admission, he was up and about, with no complaints. The reflexes were all present but decreased. He was discharged as well, with an entirely normal neurologic status on March 26, one month after admission. An electroencephalogram at this time revealed nothing abnormal.

Comment.—The first case may belong rather under the Guillain-Barré syndrome, though usually subarachnoid block is not a characteristic of this disease, either. It is suggested that these 3 cases represent various grades of the same disease, with the extremely acute, localized process in the first case and less severe, but more diffuse, disease in the others.

DISCUSSION

DR. A. M. ORNSTEEN: Did Dr. Olsen present these cases as instances of a particular disease of the central nervous system or merely as 3 clinical cases? Was the symptom picture classified? I am at a loss to discuss the condition; it might be Landry's paralysis.

LIEUT. ALEX OLSEN: The first case represents the Guillain-Barré syndrome very well except that there was complete block and operation showed a somewhat edematous cord with arachnoiditis. In the other cases the condition was simply an ascending paralysis; as far as I can gather, there were no peripheral neurologic signs, and the nerve trunks were not particularly tender or enlarged. I do not know what to call the condition in the first case. The sensory symptoms were minimal. The patient had a great deal of pain but no numbness.

DR. A. M. ORNSTEEN: Was there a time relation between the cases?

LIEUT. ALEX OLSEN: No, they were 3 successive cases, all representing degrees of the same disease, and I presented them because recovery was practically complete in all instances.

DR. A. M. ORNSTEEN: Did the patients have prodromal symptoms or avitaminosis?

LIEUT. ALEX OLSEN: The first patient had no prodromal signs whatever; the onset of the disease in the last 2 patients was preceded by an acute infection of the upper respiratory tract.

Dr. A. M. Ornsteen: In general, sporadic cases of paralysis with recession of the paralysis are not unusual, and in most instances no diagnosis is made. It is well to report as many experiences of this sort as possible, so that one may classify them and decide whether one is dealing with an avitaminosis or with a disease of degenerative or virus type. I think Dr. Olsen said a subarachnoid block was typical of the condition.

Dr. H. T. Wycis: Did Dr. Olsen mention the history of work with an unknown solvent? I remember a case in which my associates and I were unable to find what the solvent was. The man had worked for Du Pont de Nemours and Company and was in constant contact with some synthetic solvent. Ascending paralysis had developed and had terminated in a complete transverse lesion of the cord. An exploratory laminectomy revealed a thickened dura with increased venous congestion about the cord, but no other abnormality. Subsequently, he made a complete recovery.

Lieut. Alex Olsen: The paint solvent was mentioned because of the possible etiologic significance.

Dr. J. C. Yaskin: Three conditions closely simulate Landry's paralysis: (1) acute infectious polyneuritis, with irregular distribution of the structures involved and without significant abnormalities of the spinal fluid; (2) the Guillain-Barré syndrome, and (3) acute disseminated encephalomyelitis. Acute ascending paralysis usually follows the "ascending" pattern but in rare instances may be of irregular distribution, as in 2 of Dr. Olsen's cases. The diagnosis of acute ascending paralysis, like that of early multiple sclerosis, is not always easy. Perhaps the most conspicuous objective abnormality is the disappearance of the tendon reflexes. A case in my early experience taught me much. The patient previously had had a frank psychosis, with a residence of many months at the Norristown State Hospital. On admission to the Philadelphia General Hospital he complained of weakness in all limbs and went through bizarre movements in attempting to sit or to use his limbs, and in many ways his behavior suggested hysteria. His temperature, pulse and respiration were normal, but I was unable to obtain any tendon reflexes. He died suddenly, two nights after admission to the hospital. The bizarre maneuvers were undoubtedly an attempt to substitute movements by muscles which were less affected. Another patient, who was admitted several months later and who, because of the picture previously described, was regarded by the intern and resident staff as hysterical but, on instruction, was carefully watched, suddenly manifested difficulties in breathing, from which he recovered with the aid of the respirator. The early stage of Landry's paralysis is often thought to be hysteria, but the absence of tendon reflexes should put one on guard.

Lieut. Alex Olsen: In the last case I reported the physician wrote across the chart "faker."

Dr. J. C. Yaskin: Later in the course of the disease the physician is again frequently fooled in regard to the prognosis. Recovery is usually not complete for many months. One patient was discharged after many months with a gloomy prognosis, only to walk in several months later in good condition. In cases with the Guillain-Barré syndrome, in the presence of considerable protein in the spinal fluid without subarachnoid block, one must be careful in making a diagnosis in order to avoid operation.

Lieut. Alex Olsen: I have never seen an operation performed in the presence only of increased protein and no block, and I believe that most neurosurgeons, if they did operate, would do so merely to see what was there, and not with the hope of being able to help the patient. The acuteness of the onset, the high protein content and the lack of subarachnoid block would cause most surgeons to hesitate before making an exploration.

Cerebral and Spinal Operations in a Case of Severe Postencephalitic Tremors. Dr. Michael Scott.

A white woman aged 38 had had severe bilateral postencephalitic tremors with rigidity for twenty years. She had received intensive and persistent therapy with all members of the atropine group, including a preparation of belladonna alkaloids (rabellon), with gradual increase in violence of the tremor, which resulted in exhaustion and complete loss of use of both upper extremities. One year before this presentation (in April 1942) areas 4 and 6 of the hand and arm center in the right premotor area were ablated, with resulting complete cessation of the severe tremor on the left side during rest. The extremity was useless, however, being held in a position of flexion and contracture, with little movement of the arm and forearm and with slight return of intention tremor when movement occurred. The left leg could be moved only slightly, and a slight tremor was present at rest. Since the patient was able to walk three months after the operation, the loss of power in this extremity was attributed to the progressive rigidity of the disease and to rest in bed for one year. Four

months after the operation on the cortex, the pyramidal and the rubrospinal tract were sectioned on the right side at the third cervical level in an attempt to abolish the remaining severe tremor on the right side during rest. The operation on the spinal cord was decided on, first, because the speech center was in the left cerebral hemisphere and might be injured during the operation and, second, because it was thought that the results of the cerebral and the spinal operation in the same person, each done for tremor on the respective side, might offer valuable information on the comparative merits of the two procedures. Dr. N. W. Winkelman suggested that the rubrospinal tract be cut in addition to the pyramidal tract. It is now eight months since this operation on the spinal cord was done. The tremor during rest was abolished in the right upper extremity immediately after the operation and has not returned. The right forearm is held only slightly flexed, whereas the hand and fingers are held in the extended position, in contrast to the flexion contracture of the left hand and fingers. The forearm and the wrist can be flexed and extended, and similar movements can be executed to a moderate degree by the fingers. The patient can carry to her lips a small glass of water placed in her right hand without any tremor. When the hand is returned slowly to the bed, a slow, transient tremor appears and stops in a few minutes. This tremor seems to occur only when the forearm is extended. No skilled movements are possible with the right hand, the hand being held in the position of a "salute," with the movements like those of a puppet. The right lower extremity could be moved slightly after operation but is now in flexion, with extreme rigidity. The loss of power in this extremity was augmented by the deep pyramidal section. The patient's medication, which consisted of scopolamine hydrobromide, $\frac{1}{75}$ grain (0.8 mg.) every four hours when she was awake, has not been changed during the year in order that the surgical procedures might properly be evaluated.

Conclusions.—No definite conclusion can be drawn from this case as to the relative merits of the cortical and the spinal operation. Since the amount of cortical tissue removed depends on the delineation of the area by electrical stimulation, different operators will remove greater or lesser areas, with different results. The same variability applies to the depth of the spinal incision; yet this could be more accurately controlled than the extirpation.

The results to date show that either operation will abolish the tremor at rest, and they tend to confirm Putnam's opinion that pyramidal tractotomy, if confined to the fibers of the upper extremity, may offer better results than the cortical operation.

Either operation should be reserved only for patients with a tremor of such severity as to make the extremity useless. One cannot promise the patient that the hand will not be useless after the operation, although the tremor may be abolished.

Comparative observations were made after both operations with respect to tremor at rest and intention tremor, return of motor power, various reflexes, sensation and posture and final use of the extremities.

The posture of the hands and fingers following spinal section of the pyramidal and rubrospinal (?) tracts is striking, and in notable contrast to that following ablation of areas 4 and 6.

A Hoffmann sign was not obtained on the side of the pyramidal section.

Moving pictures, illustrating the patient's condition after each operation, were presented.

DISCUSSION

Dr. George D. Gammon: My associates and I recently had a patient with extreme parkinsonian rigidity and pain in the right leg on whom Putnam's operation was performed. Flaccid paralysis of the right side was maintained for five weeks; motor function is now beginning to return. The operation abolished his tremor, but he will not obtain enough voluntary power to be at all useful in either the arm or the leg.

Book Reviews

An Introduction to Group Therapy. By S. R. Slavson. Price $2. Pp. 352. New York: The Commonwealth Fund, 1943.

The author of this book is supervisor of group therapy at the Jewish Board of Guardians, a social agency in New York city which is equipped to handle psychiatric problems arising in their clientele, both individually and in groups. Although the title of the book suggests that the author might discuss group therapies in general, it is only in a short chapter near the end of the book that he briefly presents various types of group therapy. Throughout the book references are made to psychologic factors common to all forms of group therapy. The book is in the main, however, devoted to describing activity group therapy as practiced at the Jewish Board of Guardians.

The groups are usually limited to 6 or 8 persons, and at present they are made up of children whose ages fall within a 2 year span and who are less than 13 or 14 years old. The material is essentially limited to rather superficial problems of rejected children who have had some difficulty in making a social adjustment to groups in the community, whether family, school or other children. They are usually children who are somewhat over-aggressive or submissive and withdrawn, or who have bad habit formations. Psychopathic personalities and children who are extremely narcissistic, excessively sadistic or masochistic or overtly homosexual are excluded. Children who have been found inaccessible for individual psychotherapy by virtue of being rather uncommunicative are also referred for exclusive group therapy. At times the group form of treatment is used to supplement individual psychotherapy—for instance, when there is parental opposition to the latter form of treatment. Some families seem to accept the idea of the child's joining a "club" more readily than that of having him come for psychiatric treatment.

The activities of the group are varied. In the main the children are occupied with constructing whatever they desire, the material and means for doing so being made available to them. At each session refreshments are served, an occasion offering an opportunity for observation of the child in another social experience. Other activities, such as visits to museums or theaters and outings, are decided on by members of the group.

There are frequent aggressive outbursts, sometimes directed against other members of the group or against the work material. These outbursts are not interfered with by the group therapeutist, who will try to limit them only in extreme situations. The child who enters the group is accepted with all his faults and given "unconditional love." He is exposed to a permissive environment in which the expression of free activity is limited only by the other members of the group, with a minimum of interference by the group therapeutist.

A chapter is devoted to the qualifications of the group therapeutist and to the role that he should play. He is considered by the author as a catalyst, although by virtue of his age and position he does represent authority to the children. Except, however, in extreme cases, he should not use this authority, nor is he supposed to show preference to any individual members of the group or to become involved in their individual quarrels. If at times it becomes necessary to limit certain activities, the therapeutist uses the "office" as the representative of authority. On occasions, in an attempt at ego inflation in the case of a particularly beaten-down child, the therapeutist may resort to praise when this would ordinarily not be called for. Interpretations of the children's behavior are not made. In his discussion of the qualifications of the group therapeutist, the author suggests that occupational therapeutists could probably best be molded into suitable personnel.

As a result of the treatment, the child's problem-producing propensities are said to increase. The author feels that many such children have not been accepted by a group because of their own hostility toward the group. A lessening of this hostility minimizes the hostility of the environment toward him, and he therefore becomes more acceptable to the group. The development of feelings of self acceptance in the child also makes him able to accept other people. The author claims that treatment seeks to reduce anxiety arising from destructive impulses and from the fear of punishment or rejection. In general, also, the treatment aims to increase the child's tolerance to frustration. One of the potent factors in facilitating the success of group treatment is the existence in the child of "social hunger," the desire to be a part of the group and to be accepted by the group (Trotter's herd instinct [?]). As the result of this therapeutic process, there develops a group superego, which is more tolerant

and of a socializing nature. The outcome of the total experience of group therapy is a change in the ego structure of the child.

Throughout the book there are numerous case illustrations, and one chapter is devoted to a detailed discussion of 5 cases, with reproduction of actual scenes during group therapy. Although there are no statistics on the achievement of treatment, the author gives the impression that the results are rather good. It appears to the reviewer that for a limited group of patients this form of treatment might be useful. After reading the book, one has an excellent idea of the methodology of activity group therapy as practiced by the Jewish Board of Guardians.

Rehabilitation of the War Injured: A Symposium. Edited by William Brown Doherty, M.D., and Dagobert D. Runes, Ph.D. Price $10. Pp. 684. New York: Philosophical Library, Inc., 1943.

This book is a collection of articles reprinted from medical journals on every phase of rehabilitation of the war injured. These papers are arranged under the headings: "Neurology and Psychiatry"; "Reconstructive and Plastic Surgery"; "Orthopedics"; "Physiotherapy"; "Occupational Therapy and Vocational Guidance"; "Legal Aspects of Rehabilitation," and "Miscellaneous." The articles apparently are all by recognized experts in the specific fields. They are all concerned with questions of particular interest at the moment. It is of special value to physicians of the United States that so many of the papers are by leading physicians in England and present the results of experience there during the years before we in America entered the war.

The articles which bear directly on neurology and psychiatry are well chosen and are notable for the detailed information on each subject. The chapters on sequelae of war head injuries, by D. Denny-Brown, and on the rehabilitation of war head injuries, by W. McKissock and by Brigadier Hugh Cairns, offer statistics and material as yet unavailable from the wounded of our armed forces.

There is an article on treatment of speech disorders, by Stanley Cobb; one on rehabilitation after injuries to the central nervous system, by Geoffrey Jefferson, and one on the psychologic reactions to injury, dealing largely with the phantom limb concept, all of which are specifically detailed for use at the present moment.

In the sections on orthopedics and physical therapy there are several practical articles on the treatment of nerve injuries. One on the use and abuse of splints in treatment of nerve injuries, by T. P. McMurray, and one on massage and exercise in the treatment of nerve suture and repair, by James Mennell, are particularly good because of their use of sound physiologic principles, together with practical knowledge acquired from long experience. There is much that is new and interesting in the section on occupational therapy and vocational guidance. Again, the experience of the English in social rehabilitation of the war injured is of considerable value to this country at present.

The last two articles, by Lieutenant Commander James C. White, deal with the effects on the limbs of the injury, immersion and systemic changes coincidental with prolonged exposure. New syndromes are described here, and their underlying anatomic and physiologic processes are outlined. There are many details as to the effects of various treatments.

In general the book is excellent. It presents in a relatively small space the reports of experts on many aspects of rehabilitation. The detail is such that those seeking practical information may obtain it, and the scope of articles is sufficiently wide that they may be of interest to the civilian neuropsychiatrist at any time, as well as to the medical officer in the present emergency. The bibliography is useful and usable. There are few symposiums which so effectively accomplish their aim. The editors are to be complimented particularly on their choice of authors, which necessitated a wide knowledge of the field, and one not usually found in a time of emergency such as the present.

The faults of this book are minor. It is poorly proofread, and the photographs are scarcely worth their space. It would have been relatively simple to have given more detail to the position and capacities of the authors, some of whom are mentioned only by name, without title, and this would have added both interest and weight to what they have written.

Physiological Psychology. By Clifford T. Morgan. Price, $4. Pp. xii plus 623, with 176 illustrations. New York: McGraw-Hill Book Company, Inc., 1943.

Morgan devotes about two thirds of his excellent book to the background of psychology, to the anatomy and physiology that make psychology possible. Much of this material is already in the books on neurophysiology, but the point of view and the control that the author exerts over his material are valuable and interesting, as well as soundly developed. The author enjoys a peculiar position, indeed, being able to draw on the findings not only

of the medically inclined physiologists but of workers in more academic realms. In any event, the conclusions are emphasized by numerous charts and curves that reveal the basic mechanisms involved.

The book follows the conventional pattern in presenting material concerning the development and differentiation of the nervous system and its functions, with special chapters on the various senses, marking considerable recent advances in scientifically controlled experiments. Chapters on emotion, sleep and activity, instinctive behavior, mating behavior and bodily needs serve to facilitate the transition to an excellent "Survey of Adaptive Behavior," which is the author's most distinctive and personal contribution. Here he is able to collect, integrate and expand the ideas of numerous predecessors, beginning with Claude Bernard, on the humoral motive factor and the central motive state that underlie a large proportion of the strivings and total behavior of the living human organism.

"The *set* aspect of motivation, *i. e.*, the potentiality of perceiving various aspects of the external situation and reacting to them in an organized way, is dependent chiefly upon the cerebral cortex. Without the cortex, the motive state eventuates only in the immediate general and specific forms of behavior associated with the c.m.s., or humoral motivating influence giving rise to it; the more complex perceptions and organized responses which issue from the priming property of the c.m.s. are lacking." This summary introduces a survey of learning that reaches into the field of psychology itself, including symbolic processes.

The author admits that he has tried to get away from the armchair type of psychology, or the subjective method of approach, and consequently has relied mostly on animal experimentation, pointing out again and again special experiments that should be performed in order to test the theories developed. In some ways, therefore, the book lacks the charm of personal experiences and their physiologic correlates. If there is one field in experimental psychology that has been slighted in the book, it is that of experimental neuroses, which receives only two pages. A bibliography of 830 references, together with an excellent index, renders this work particularly valuable for the advanced student.

The Nature and Treatment of Mental Disorders. By Dom Thomas Verner Moore, O.S.B., Ph.D., M.D., with a foreword by Edward A. Strecker, M.D. Price, $4. Pp. viii, plus 312. New York: Grune and Stratton, Inc., 1943.

Father Moore, from his long experience as both priest and physician to the mind, makes in this book a "sincere attempt to make use of whatever is available in psychology or physiology to clarify the concept of mental disorder or ameliorate any abnormal condition of the human mind." "Successful psychiatry," he continues, "can neglect neither the psychic nor the somatic." While he does not specifically emphasize the power of God, this factor is the constant K that enters into almost every equation of human personalities that so richly illustrates this small, readable volume.

The book starts off with a brief and succinct summary of the various concepts of psychopathology held by Freud, Jung, Adler and Alexander, with critical comments concerning their lack of control observations. "It is high time for psychoanalytic writers to test their theories of the origin of mental disorder by empirical study and statistical procedures." Dr. Moore's own tetrachoric correlations leave something to be desired in the way of precision in definition of symptomatology, although in his previous works, to which he refers repeatedly, the characteristics investigated are evidently more thoroughly analyzed. It suffices in the present volume for the author to find a certain correlation between "stereotypism of attitudes," "giggling" and "loss of finer sensibilities" picturing in the syndrome of schizophrenia. By means of these intercorrelations, the author presents an apparently novel syndrome, paranoia irritabilis.

The book is somewhat of the "closed compartment" type, with discussions of these statistical studies and the erection of syndromes, contrasted with references to the physiologic foundations of emotional expression and hypothalamic activity, on which is engrafted a psychotherapy as eclectic as the best, with the beneficence of God as an explanation for some of the otherwise inexplicable successes recounted. It must be accepted as a personal, almost autobiographic, account of adventures in psychopathology and psychiatry by a man who has experienced two fundamentally different disciplines and who attempts, with mottlings of success and failure, to bring the two into greater harmony. Since this volume cannot be considered a textbook of psychiatry of any pretensions, it is incongruous to find some 30 pages devoted to standard nomenclatures of disease as applicable to psychiatry.

STUDIES IN REFLEXES

HISTORY, PHYSIOLOGY, SYNTHESIS AND NOMENCLATURE: STUDY I

ROBERT WARTENBERG, M.D.

SAN FRANCISCO

The subject of this clinical and literary study is a discussion of some of the diagnostically most important reflexes from a practical neurologic standpoint. It deals with their history, physiology, technic of elicitation, synthesis and nomenclature, with emphasis on the synthesis of the existing reflexes and the simplification of their nomenclature.

In 1927, a leading Polish neurologist,[1] in an abstract of a Russian article on reflexes, said:

In any event, in view of the wealth of reflexes to be elicited from the soles of the feet, which in summer are usually dirty, the practitioner should be extremely grateful to the neurologist who would contribute something concrete to the unification and understanding of the physiogenesis of these reflexes; he would thus spare the clinician the necessity of examination for most of them.

On the same page, a German neurologist,[2] in discussing a Polish study on reflexes stated:

. . . It is gratifying that now, from several angles, the rediscovery of reflexes is undergoing critical scrutiny. . . . Indeed, there would soon be more reflexes, especially of the lower extremities, than there are muscles and bones. A systematic synthesis would be appropriate.

An attempt at such a synthesis is made here. Dorland[3] lists nearly two hundred and fifty reflexes, and a few more are given under the

heading of "Signs." Seventy-six new pathologic reflexes were described in the period from 1918 to 1943, according to the statistics of Fröhlich.[4] No wonder then that the reader of neurologic textbooks, journals and hospital charts is confused and puzzled by the descriptions of reflexes he finds there. He meets a great number of unfamiliar eponyms, which often are not contained in any medical dictionary or textbook. Various authors attribute the discovery of the same reflex to different persons and name it accordingly. A single reflex may be named according to the site of its elicitation, the muscles involved, the ensuing movement, the joint on which it acts or the nerves involved. Some reflexes are called signs or phenomena; some are designated by a proper name only, occasionally with an attached numeral. Thus one may read: "Bechterew 2 is negative," or "Bing 1 and 2 are strongly positive." To the authors of these names, that which is conveyed by them is self explanatory—not so to the reader. A leading European neurologist, in reporting a case in 1937, used in a single paragraph, and without further comment, fourteen proper names (including his own) to describe the reflexes in his case. Many an author, in his enthusiasm over the discovery of what he thinks is a new reflex, does not correlate his reflex with the phenomena already recognized. It is thus not clear whether the "new" reflex is a new phenomenon at all or whether it represents merely a new technic by which an old and familiar reflex is brought to light. Thus it happens that the old reflexes have been rediscovered several times, and many a "recently discovered" reflex is actually only a modification of an old one or a combination of multiple reflexes.

Many a reflex has been "discovered" by one author after another, often at intervals of several decades. These authors, anxious to attach their own names to a "new" reflex, have neglected completely the work of their predecessors. The

1. Markov, D.: Receptorenzonen für Reflexe vom Typus Mendel-Bechterew-Rossolimo-Žukovskij-Kornilov, Sovrem. psichonevrol. **3**:64, 1926; abstracted by Higier, H.: Zentralbl. f. d. ges. Neurol. u. Psychiat. **45**:726, 1927.

2. Sagin, K.: Der Reflex des "Malleolus externus" und das Piotrowskische Phänomen, Monatschr. f. Psychiat. u. Neurol. **61**:188, 1926; abstracted by Loewy-Hattendorf, E.: Zentralbl. f. d. ges. Neurol. u. Psychiat. **45**:726, 1927.

3. Dorland, W. A. N.: The American Illustrated Medical Dictionary, ed. 19, Philadelphia, W. B. Saunders Company, 1941, p. 1230.

4. Fröhlich, J.: Die Bereicherung unserer Kenntnisse über. pathologische Reflexe in den letzten 15 Jahren, Inaug. Dissert., Basel, 1935.

history of reflexes provides an interesting chapter in the book of human vanity—a chapter often not lacking in tragicomic elements.

Many a phenomenon which is not at all reflexive in its character is designated as a reflex. In a recently published book, for instance, the leg sign of Barré is wrongly called a reflex. With this valuable sign of hemiplegia, the patient, while lying prone on his stomach with his legs flexed to a vertical position at the knee, is unable to maintain this position on the side of the pyramidal lesion and gradually extends the affected leg. This phenomenon is of course not a reflex but simply a motor response to the inequality in strength of the extensor and flexor muscles of the legs in hemiplegia. In a recently published textbook, the diminution of the palpable vibrations of the orbicularis oculi muscle associated with facial palsy of long standing has been designated as a reflex. This phenomenon is by no means a reflex but is simply an expression of decreased innervation. In a reference book published in 1939, the platysma sign of Babinski is called a reflex, whereas it simply indicates the weakness of the platysma muscle on the side of hemiplegia.

Much further confusion has been caused by the fact that true deep muscle reflexes are not always distinguished from reflex phenomena which belong in quite a different category, i. e., associated movements, reflexes of spinal automatism, defense reflexes and postural reflexes. The "new tendon stretch reflex," recently described by Gonda,[5] is in fact a modification of the Marie-Foix maneuver for elicitation of the flexor withdrawal reflex. This is a postural, a coordinated, reflex, and not a muscle stretch reflex (Wartenberg[6]). Furthermore, the distinction between the so-called deep and the superficial reflexes is not always made clear.

Much has been done in standardization of the nomenclature of disease, but little in standardization of the terms used to designate signs and symptoms and less in description of the numerous reflexes. At present there is no need for more reflexes or for more variations in the technic of their elicitation. The last decades brought a real "inflation" in this respect. What is actually needed is a simplification, a synthesis and correlation of the many reflexes already in existence. The mere listing of the reflexes, together with their various proper names, as practiced in many a textbook, imposes a great burden on the student and does not in any sense present an appropriate physiologic approach to the problem.

For the preparation of this paper, which attempts a systematic synthesis of some of the numerous deep reflexes, the literature, especially the earliest, which appeared in six languages, including the Russian, was studied in the original. This review of the literature, though extensive, is of course by no means exhaustive. Such a survey would have required volumes. Moreover, war conditions necessitated a sharp curtailment in the original plan for a monographic presentation of the subject.

BASIC PRINCIPLES

For a basic understanding of the problem, I shall first outline in brief form a few general tenets applicable to all reflexes under discussion.

1. It is permissible from a physiologic standpoint to assume that every striated muscle, as it contracts on direct mechanical, electrical or voluntary stimulation, contracts also on reflexive stimulation. The most important reflexive stimulus of the muscle consists of a sudden, brief concussion and stretching of the muscle tissue. Here the most essential stimulus—perhaps the only one—is a sudden, quick pull, exerted longitudinally. The emphasis lies on the sharpness and brevity of the stroke. A slow stroke, even though its range is greater, is ineffective. The muscle reacts to this sudden stretching with contraction, which constitutes what is called the deep, or tendon, reflex. In general, when one speaks of a deep reflex as a muscle stretch reflex, one has in mind a sudden, brisk stretching, a jarring of the muscle, so to speak, and not a slow stretching, which leads to a change in position. Many other reflex phenomena, such as associated movements, postural reflexes and support reactions, are elicited through change in position, that is, in a practical sense, through stretching of some muscles. But such responses are not in any sense the muscle stretch reflexes which are discussed here. Foerster wrongly criticized Hoffmann's concept of the reflexes since he did not differentiate clearly between these two types of muscle stretch phenomena. Nearly all striated muscles can be reflexively stimulated by quick stretching. Lastly, such a reflex has been demonstrated in the diaphragm (Trömner[7]). Only from the ocular muscles, thus far, have such reflexes not been obtained.

2. These muscle stretch reflexes serve, and did serve still more earlier in phylogenetic development, as a useful protective mechanism,

5. Gonda, V.: A New Tendon Stretch Reflex, Arch. Neurol. & Psychiat. **48:**531 (Oct.) 1942.

6. Wartenberg, R., in discussion on Gonda, V.: A New Tendon Stretch Reflex and Its Significance in Lesions of the Pyramidal Tracts, Tr. Am. Neurol. A. **68:**111, 1942.

7. Trömner, E.: Ein (neuer) Zwerchfellreflex. Deutsche Ztschr. f. Nervenh. **102:**157, 1928.

especially in standing and walking. They have the task of fixing the position of the joints and of counteracting quickly the influence of every sudden external agent that changes the position of the joint. Some muscles react with contraction more easily and strongly to stretching than others, the threshold of response depending on their function. Muscles which are physiologically stronger than their antagonists, as well as muscles which show a greater tendency to contraction in spastic paralysis, respond more easily to passive stretching. The extensor muscles of the legs (the quadriceps muscle and the muscles of the calf) show better developed deep reflexes than the flexor muscles. Undoubtedly this difference has to do with their function in the maintenance of correct posture in standing and walking. Normal, rapid function of the quadriceps reflex will prevent, compensate for and ease any sudden, momentary collapse of the body and is essential for correct posture. A quick reflexive contraction of the muscles of the calf on being stretched will prevent the body from falling forward; contraction of the flexors of the toes will help the foot to clinch the ground when the body's balance is endangered. In the arms, the reflexes of the pronators are more excitable than those of the supinators. Some muscles are so situated that they are mechanically more accessible to passive stretching than others.

3. The strength of the reflex action of the various muscles of any person thus differs widely. This strength also varies greatly from one person to another. Some normal persons show deep muscle reflexes only in traces, even with the most delicate technic. The contraction of a muscle on being stretched may exist in latent form and become distinct, or apparent at all, only when there is a functional or an organic increase in muscle tonus. Thus, a pyramidal lesion may (*a*) increase the existing reflexes and (*b*) bring the reflexes which are latent to the fore. Here the presence of these reflexes does not of itself mean the presence of a pyramidal lesion, though the reflexes are especially likely to appear if such a lesion exists. It is essential, therefore, to keep in mind the fact that the appearance of some reflexes—usually latent—in the presence of a pyramidal lesion does not mean that the reflexes are new, but rather that they represent the pathologic exaggeration of normal reflexes which exist in latent form. Thus, if a reflex, usually latent, is clearly seen, it may indicate a pyramidal lesion, but not necessarily so. From the standpoint of diagnosis, this point should be stressed.

4. Since concussion of the muscle and its stretching constitute the true cause of the deep muscle reflex, the point from which this response may be achieved is not essential. It is irrelevant whether the concussion comes from the tendon, from the neighboring joints or from bone, or is obtained through a broad mass percussion of the muscle itself. No point has any monopoly; every muscle can be stretched, and its reflex contraction is effected from many points. In cases of hyperreflexia even a slight concussion—direct or indirect—of the bone to which the muscle is attached is sufficient to provoke its reflexive contraction.

5. Every muscle crosses one or more joints and is therefore comparable to a tautly drawn bowstring. Sudden stretching of such a string may be achieved by a force acting either on the plane or on the convex side of this bow mechanism. The tapping of the muscle itself, of its point of origin or of its point of insertion corresponds to the tapping of the taut string at any of its points. But one is able to effect a stretching of the string also by tapping the convex side of the bow mechanism, especially at its top. One depresses the top of the arch and thus causes a sudden stretching of the bowstring, representing the muscles. This possibility of elicitation of a deep muscle reflex, not by attack on the muscle itself but by stimulation on the convex side of the arch—the bone—deserves to be stressed, since it offers much to the comprehension of many misunderstood and misnamed reflex phenomena.

6. The concussion and stretching of a muscle that leads to its reflex contraction can be achieved not only from points located directly on either side of the "arch" but from neighboring, and even distant, points. Here the bone acts as transmitter of the mechanical insult. It is possible to elicit the reflexes from remote places, particularly in cases in which there is functional or organic reflex hyperirritability. The older neurologists, in referring to such cases, spoke of "an extension of the reflexogenous zones"—an incorrect and misleading term.

7. The transmission of concussion through the bone makes it understandable that under favorable conditions a single tap with the reflex hammer may affect several functionally different muscles and thus evoke multiple, but completely independent, unrelated reflexes. One is apt to overlook this possibility in eliciting a particular reflex, since the attention is concentrated on the action of the corresponding muscle. Practically, however, one often elicits more than one reflex more or less distinctly, the complexity of the response depending on the position of the limb, the strength and direction of the stroke, the relative strength of the reflexes and the

degree of general reflex irritability. Moreover, one might even say it is difficult to avoid elicitation of multiple reflexes with a single tap and to obtain the desired effect on a single muscle.

8. Since each of the clinically important reflexes can be elicited, even in normal persons, in three, four, or even more, ways, a boundless confusion would result if every such possible reflex elicited were dubbed a special reflex and given a specific, or even a proper, name. The tendency should be to name the reflex according to the acting muscles, not the point of stimulation. For a given reflex the muscle is always the same, but the place of stimulation may vary considerably. It is clinically essential to know whether the reflex is present, altered or absent, but it is not necessary to know from which point this can be demonstrated. If, in describing the reflexes, one wishes to be exact, one may note the special technic of their elicitation without resorting to new or proper names.

If, in interpreting and naming the reflexes, one shifts the focus of attention from the point of elicitation to the muscle whose action is provoked, an essential simplification, a better physiologic understanding and a distinct didactic advantage result. Then the existing reflex phenomena may be easily assigned to their proper places, future discoveries in this field may be readily appraised and classified and the uncritical discovery of "new" reflexes may be checked. While the abolition of proper names in the nomenclature of reflexes is generally favored, it is still well to apply them temporarily to really new reflexes or in exceptional or classic phenomena. The Babinski toe sign may represent such a reflex.

9. What has been said thus far refers to the so-called deep reflexes, which are often designated as tendon, bone, periosteal, osteoperiosteal, osteotendon, joint, fascial or aponeurotic reflexes. Since the investigations of Sternberg,[8] in 1893, and of Hoffmann,[9] in 1922, it has been known that the receptors of the "tendon and periosteal" reflexes lie not in the tendon or in the periosteum but in the muscle itself. Yet, in a recent article, Guillain[10] said: "The tendon and periosteal reflexes are abolished." In the most recent Spanish textbook of neurology, Barraquer Ferré, de Gispert Cruz and Castañer

Vendrell[11] distinguished between tendon reflexes and osteoperiosteal reflexes. In another Spanish textbook, published in 1939, Litter and Wexselblatt[12] spoke of tendon and periosteal reflexes. Even Kinnier Wilson, in his fundamental work on neurology, spoke of bone and tendon reflexes. It is extremely difficult, to be sure, to find an appropriate adjective in which is condensed the meaning of such a complex phenomenon as a reflex. But these terms, though widely used, are objectionable since they are not in accordance with the modern, physiologically based concept of the nature of these reflexes. The time-honored term "tendon reflexes," introduced by Erb in 1875, is especially misleading and should not be used at all. From a neurophysiologic standpoint the tendon, so to speak, is passive, dead tissue, and no stimulation of the tendon can evoke any reflex action unless the muscle tissue is influenced through the tendon. There is no such thing as a "tendon stretch reflex." One can elicit the deep reflexes without touching the tendon—for instance by tapping the patella downward to obtain the quadriceps muscle reflex. Furthermore, reflexes can be obtained in muscles having no tendons, such as the masseter muscle. Long ago Gowers[13] emphasized that the intervention of tendons is not necessary for the production of "tendon reflexes." The importance of the tendon lies only in the fact that, like a bridle, it controls the whole muscle by presenting a tough, small bundle, which takes little space and is easily accessible to the stroke of the reflex hammer. Thus the muscle tendon serves only as a transmitter of the stretch stimulus from the point of application to the muscle fibers. Gowers pointed out that the one condition which all "tendon reflexes" have in common is the passive tension which is essential for their occurrence, and he also suggested that they be termed myotatic contractions —from the Greek word τείνειν, meaning to "extend." Earlier in 1880, Gowers[14] stated that the term "tendon reflex" is inaccurate and misleading. He asserted that the achilles reflex is essentially a muscle reflex phenomenon and not a tendon reflex.

It is hardly necessary to elaborate on the fact that the reflexes in question are not periosteal,

8. Sternberg, M.: Die Sehnenreflexe und ihre Bedeutung für die Pathologie der Nervensystems, Leipzig, F. Deuticke, 1893.

9. Hoffmann, P.: Untersuchungen über die Eigenreflexe menschlicher Muskeln, Berlin, Julius Springer, 1922.

10. Guillain, G.: Radiculoneuritis with Acellular Hyperalbuminosis of Cerebrospinal Fluid, Arch. Neurol. & Psychiat. 36:975 (Nov.) 1936.

11. Barraquer Ferré, L.; de Gispert Cruz, I., and Castañer Vendrell, E.: Tratado de enfermedades nerviosas, Barcelona, Salvat Editores, S. A., 1936-1940.

12. Litter, M., and Wexselblatt, M.: Tratado de neurologia, Buenos Aires, El Ateneo, 1939.

13. Gowers, W. R.: A Manual of Diseases of the Nervous System, ed. 3, Philadelphia, P. Blakiston's Son & Co., 1907, vol. 1, p. 26.

14. Gowers, W. R.: Diagnosis of Diseases of the Spinal Cord, London, J. & A. Churchill, 1880, p. 25.

either in origin or in mode of elicitation. The deep reflex cannot be abolished even if the sensibility of the periosteum has been completely eliminated by procaine. The so-called radio-periosteal reflex is not periosteal at all. It is a stretch reflex of the brachioradialis muscle. The periosteum is only the point of application of the stretch stimulus. There are likewise among the deep reflexes no fascial, bone or joint reflexes. The sensibility of the joints, for instance, does not play any role. These structures serve only to transmit the stretch stimulus. The deep reflexes are physiologically muscle stretch reflexes and should be so called. But the custom and brevity make it desirable to retain the old term "deep reflexes."

10. Reflexes which do not fit into the regular reflex pattern are often called "paradoxic," "inverted" or "antagonistic." These terms should not be used. There is nothing paradoxic, inverted or antagonistic about them. It will be shown in the discussion of individual reflexes that these phenomena are simply occasional forms of well known deep reflexes appearing under certain conditions and depending on particular technics applied in their elicitation. They are easily understandable, normal phenomena.

11. The second large group of reflexes are called superficial, or "skin," reflexes, in contrast to the deep reflexes. Hoffmann called them *Fremdreflexe,* since the stimulus initiating the contraction is applied not to the muscle itself but outside the muscle. In the superficial reflex a stimulus applied to the skin, without directly involving the mass of the muscle, evokes the reflex contraction of the muscle. Such a reflex is neither a muscle stretch reflex nor muscle-muscle reflex but a skin-muscle reflex. It is not a direct, but an indirect, muscle reflex; it is not intrinsic but extrinsic, or one might say "referred." It is not always local, and may be distant. The superficial reflexes differ from the deep reflexes in that they are evoked by a greater variety of stimuli; their "reflexogenous zones" are much more extended; their latent period is longer and is dependent entirely on the strength of the stimuli, and on their summation; their fatigability is greater. Whereas every muscle has its deep muscle reflex, only a few muscles have their superficial reflexes as well.

METHODS OF REENFORCEMENT

Of all the problems of the technic of reflex elicitation, only the methods of so-called reenforcement will be discussed here. The goal of these methods is to make a slight reflex more apparent and one seemingly lost perceptible. It

is a common mistake to regard the reflex as lost when it is not. The methods of reenforcement which bring the reflex to light often help to avoid this error, with all its momentous diagnostic implications.

The deep reflex is a delicate and sensitive mechanism and is highly susceptible to the slightest external influence. Suffice it to mention that the tabetic patient who shows no reflexes when sober may manifest them while under the influence of alcohol, and that the knee jerk, for instance, increases the moment the patient falls asleep and decreases when he is in deep sleep (Ferguson [15]). The methods which facilitate the appearance of the deep reflexes are numerous and varied. Feix [16] and Trepiccioni [17] found that the best position for the patient during examination for deep reflexes was that in which he lay on his side, with legs bent at the hip and at the knee joints. If no response was obtained, the following means might be employed: better support of the limb, change of position, repeated passive movement and increased stretching of the muscles in question. The muscles may be struck, in preparation, by a hammer or be mildly massaged. When the patient keeps his muscles tense, the muscle stretch reflex can hardly be perceived; therefore the patient should be instructed to relax. Different methods may be used to distract his attention: He may carry on a conversation, look at a picture or stare at the ceiling, count, compute small sums, read aloud and fast, repeat the Lord's prayer or listen to music. Or the eyes may be examined simultaneously. Some investigators recommend slight sensory stimuli, such as a needle prick, a light flashed in the eyes, a cold or warm bath, massage or diathermy. For reenforcement of the knee jerk Plesch [18] used transverse compression of the patella and the tendon of the quadriceps muscle and the pinching of a fold of skin above the patella. Saggese [19] recommended quick pressure on the larynx and the upper part of the trachea from both sides, the thumb and index finger being used. Schreiber [20] advocated mild mas-

15. Ferguson, J.: Some Additional Remarks on Knee-Jerk, M. Rec. **4**:267, 1893.

16. Feix, J.: Ueber ein neues Verfahren zur Untersuchung des Patellar- und Achillessehnenreflexes, Wien. klin. Wchnschr. **19**:1223, 1906.

17. Trepiccioni, E.: Una nuova maniera di provocare il riflesso rotuleo, Policlinico (sez. prat.) **38**:6, 1931.

18. Plesch, J.: Handgriff zur leichten Auslösung des Kniesehnenreflexes, München. med. Wchnschr. **70**:637, 1923.

19. Saggese, V.: Una manovra per esaltare in particolari casi il riflesso patellare, Riv. di clin. pediat. **32**:1159, 1934.

20. Schreiber, J.: Ueber das Knie-Phänomen, Deutsches Arch. f. klin. Med. **35**:254, 1884.

sage of the forelimb and repeated tapping of the tendon. Various other sensory stimuli have been recommended. Electrical stimulation was used by Knapp,[21] Boettiger [22] and Lewandowsky and Neuhof [23]; vibration was employed by Stscherback.[24]

Some maneuvers for reenforcement of the deep reflexes consist of active, forcible innervation of remote muscles on the part of the patient. Jendrassik,[25] in his famous method, recommended examination of the knee jerk at the moment the patient pulls his hooked hands apart. Laufenhauer, cited by Pándy,[26] asked the patient to squeeze the upper part of the physician's arm; Schoenborn [27] had him squeeze the examiner's left hand. The method of Krönig [28] requires the patient to draw in his breath deeply and quickly. Popper [29] and Marcus [30] suggested coughing and Kroner [31] recommended a short walk. Montemezzo [32] requested that the patient forcibly bend his trunk. Jendrassik,[33] and later Justman [34] and Weatherby,[35] recommended that the patient press down the thigh during exami-

nation for the knee jerk. They assumed that during this act the innervation of the antagonists would decrease the tonus of the quadriceps muscle. Faulkner,[36] on the same assumption, recommended that the patient, while lying in a supine position, press his heels against the bed. Balaban [37] requested the patient to press the ball of the foot against the left hand of the examiner. On the basis of the examination of 1,150 patients, Kostin [38] found that the patellar reflex can be elicited by the method of Balaban more easily than by any other means. Grinker [39] stated:

An excellent method to obtain reinforcement of the knee jerk is to have the subject, with knees slightly flexed, gently press the ball of his foot against the examiner's free hand.

Krueger [40] let the patient hang his legs over the edge of the table, the calf resting against the edge, so that a 45 degree angle was formed. Here the weight of the legs has the same effect as the pressing down of the heel. The methods of Salomon [41] and Stevenson [42] consisted in active plantar flexion of the foot and toes; the method of Weidlinger,[43] in active lifting of the heel. Shvetzow [44] recommended tapping of the ligamentum patellae at the same moment that the patient makes an active dorsiflexion of the homolateral foot. The procedure of Negro [45] is similar: The patient, his heel placed on the floor, dorsiflexes his foot, and the examiner simultaneously exerts pressure on the thigh. The procedure, according to Negro, is intended to increase the tonus in the quadriceps muscle.

The explanation for the effectiveness of all these maneuvers is that they divert the attention of the patient. This helps him to relax the muscles he may have held in high tension, so

21. Knapp, A.: Kniephänomene und ein neuer Kunstgriff zu ihrer Auslösung bei multipler Neuritis (Pseudotabes polyneuritica), München. med. Wchnschr. **87**:749, 1940.

22. Boettiger, A.: Ein neues Hilfsmittel zum Nachweise schwächster Sehnenreflexe, Neurol. Centralbl. **29**:122, 1910.

23. Lewandowsky, M., and Neuhof, H.: Ueber Wiederbelebung der Reflexe, Ztschr. f. d. ges. Neurol. u. Psychiat. **13**:444, 1912.

24. Stscherback, cited by Lewandowsky, M.: Handbuch der Neurologie, Berlin, Julius Springer, 1910, vol. 1, p. 587.

25. Jendrassik, E.: Zur Untersuchungsmethode des Kniephänomens, Neurol. Centralbl. **4**:412, 1885.

26. Pándy, K.: Die Kraft der Sehnenreflexe und die Veränderung derselben bei der Hemiplegie, Neurol. Centralbl. **23**:449, 1904.

27. Schoenborn, S.: Bemerkungen zur klinischen Beobachtung der Haut- und Sehnenreflexe, Deutsche Ztschr. f. Nervenh. **21**:273, 1902.

28. Krönig, G.: Ein einfacher Kunstgriff zur Erzeugung des Kniephänomens, Berl. klin. Wchnschr. **43**:1421, 1906.

29. Popper, E.: Zur Kenntnis des Patellarreflexes, Deutsche Ztschr. f. Nervenh. **67**:131, 1920.

30. Marcus, I. H.: Coughing: A Method of Reenforcing the Knee Jerk Reflex, Arch. Neurol. & Psychiat. **34**:1295 (Dec.) 1935.

31. Kroner, cited by Lewandowsky, M.: Handbuch der Neurologie, Berlin, Julius Springer, 1910, vol. 1, p. 587.

32. Montemezzo, A.: Sul reflesso rotuleo: semplice espediente a facilitarne il rilievo, Scritti di sc. med., 1923, p. 239.

33. Jendrassik, E.: Beiträge zur Lehre von den Sehnenreflexen, Deutsches Arch. f. klin. Med. **33**:177, 1883.

34. Justman, S.: Sur une nouvelle méthode pour obtenir le réflexe rotulien, Rev. neurol. **30**:225, 1923.

35. Weatherby, E.: The Justman Method of Eliciting the Knee-Jerk, Mil. Surgeon **89**:902, 1941.

36. Faulkner, J. M.: A Simple and Effective Method of Reenforcing the Knee Jerk, Arch. Neurol. & Psychiat. **28**:895 (Oct.) 1932.

37. Balaban, J. M.: Méthode d'exploration du réflexe rotulien, Arch. internat. de neurol. **56**:287, 1937.

38. Kostin, A.: Examination of the Patellar Reflexes by the Method of Dr. Balaban, Sovet. nevropat. **4**:170, 1935.

39. Grinker, R., in Tice, F.: Practice of Medicine, Hagerstown, Md., W. F. Prior Company, Inc., 1925, vol. 9, p. 259.

40. Krueger, E.: Zur Erleichterung von Reflexprüfungen, München. med. Wchnschr. **2**:1273, 1939.

41. Salomon, E.: Eine zweckmässige Art den Patellarreflex auszulösen, Neurol. Centralbl. **30**:80, 1911.

42. Stevenson, F. E.: Reenforcement of the Knee Jerk in Children, Arch. Neurol. & Psychiat. **31**:614 (March) 1934.

43. Weidlinger, E.: Empfindliche Methode zur Auslösung des Patellarreflexes, Med. Klin. **29**:847, 1933.

44. Shvetzow, S. P.: On the Mechanism of Artificial Stimulation of the Knee Jerk, Sovet. nevropat., psikhiat. i psikhogig. **1**:591, 1932.

45. Negro, C.: Di una particolare modalità tecnica di esplorazione del fenomeno del ginocchio, Gior. di med. mil. **69**:598, 1921.

that the appearance of the reflex is facilitated. Further, it is thought that active innervation of antagonist muscles serves to bring about a reflexive relaxation in the muscles in question. While this is true, observers, on the other hand, have come increasingly to realize that without a certain tension in the muscles in question no reflex will appear. The efficiency of some of the described maneuvers has therefore been sought in the fact that active innervation of neighboring, antagonistic or remote muscles brings about a slight, involuntary increase in the tension of the muscles in question, which results from an overflowing of the impulse. This increase of muscle tension facilitates the work of the reflex mechanism, increases the strength of the reflex or allows it to appear at all.

Another point is worth mention. In patients with lesions of the pyramidal tract, associated movements appear in the affected limbs on voluntary muscular effort of any kind. These associated movements, for instance those in the leg, are similar to movements which may be produced by elicitation of the knee or ankle jerk. It is thus conceivable that through effort of any kind these associated movements appear in mild or subclinical form. They support the reflexive movement, since the results of the two types are the same; in the leg, for instance, they both produce extension.

Another neglected point in the discussion of the effectiveness of the aforementioned maneuvers may be briefly considered here. From clinical experience and from experiments (Montgomery and Luckhardt[46]), it is known that pronounced increase of intracranial pressure brings about prompt diminution or abolition of the knee jerk. Aird[47] showed, however, that a slight increase of intracranial pressure, such as that produced by prolonged jugular compression, will make the deep reflexes more apparent. Since some of the maneuvers mentioned for reenforcement of the deep reflexes, such as pulling the hooked hands apart, coughing or bending the trunk, are accompanied by notable increase in intracranial pressure, it is quite justifiable to assume that this increased pressure may contribute to the appearance and augmentation of the reflexes.

On the basis of his studies of action currents of the muscles, Hoffmann[48] stressed that complete voluntary relaxation of the muscles diminishes the characteristic action currents which normally appear with deep reflexes. Conversely, the action currents of the deep reflexes increase during voluntary contraction of the muscles. Weber[49] recently proved that this is true also for the masseter reflex. The simultaneous, voluntary innervation of the muscle through which the reflex is carried opens the gateway for this reflex. Weber observed that when the innervation of the muscles in question is lessened, the reflex decreases, and that it finally disappears when the antagonistic muscles are innervated. On the basis of these observations on sensitization of the reflex through mild active innervation of the muscles in question, Hoffmann recommended slight voluntary innervation of the corresponding muscles for reenforcement of the deep reflexes. In accordance with this view, von Weizsäcker[50] explained the efficiency of the maneuvers of Jendrassik and others in the following way: Through such a maneuver, a muscle which has been overly tense becomes less tense; on the other hand, a completely relaxed muscle receives overflowing impulses from remote muscles which are actively innervated. This facilitates the elicitation of the reflex. On the basis of physiologic experiments with the patellar reflex, Sommer[51] concluded that with the maneuver of Jendrassik a stimulus is reflexly transmitted from the excessively innervated muscle groups to the quadriceps muscle. This stimulation acts in the same way as stretching of the whole muscle and thus increases the susceptibility of the quadriceps muscle to further, passive stretching. In this connection, it is worthy of note that in case of hysteria, with complete muscular relaxation, the deep reflexes may transiently be absent (Nonne[52] and Wohlwill[53]). They may even be diminished under the influence of rest or mere ideas of sleep (Karger[54]). It was found in physiologic experi-

46. Montgomery, M. F., and Luckhardt, A. B.: Studies on the Knee Jerk: VIII. The Effects of Acutely Raised Intracranial and Intraspinal Pressures upon Knee Jerk, Am. J. Physiol. **91**:210, 1929.

47. Aird, R. B.: Prolonged Jugular Compression, Arch. Neurol. & Psychiat. **45**:633 (April) 1941.

48. Hoffmann, P.: Die physiologischen Eigenschaften der Eigenreflexe, Ergebn. d. Physiol. **36**:15, 1934.

49. Weber, W.: Physiologische Untersuchungen über den Masseterreflex beim Menschen, Deutsche Ztschr. f. Nervenh. **144**:160, 1937.

50. von Weizsäcker, V.: Neuere Forschungen und Anschauungen über Reflexe und ihre physiologische Bedeutung, Klin. Wchnschr. **1**:2217, 1922.

51. Sommer, J.: Periphere Bahnung von Muskeleigenreflexen als Wesen des Jendrassikschen Phänomens, Deutsche Ztschr. f. Nervenh. **150**:249, 1940.

52. Nonne, M.: Zwei durch zeitweiliges Fehlen des Patellarreflexes ausgezeichnete Fälle von Hysterie, Deutsche Ztschr. f. Nervenh. **24**:474, 1903.

53. Wohlwill, F.: Ueber funktionell bedingtes Fehlen der Patellarreflexe, Neurol. Centralbl. **28**:567, 1909.

54. Karger, P.: Reflex, Wille und Vorstellung, Klin. Wchnschr. **3**:2273, 1924.

ments (Jacobson and Carlson[55]) that the knee jerk decreases constantly with progress in relaxation and that in some subjects a degree of relaxation could be obtained in which the knee jerk was abolished without the subject's going to sleep. All this demonstrates clearly the influence of active innervation of the muscles on the so-called tendon reflexes.
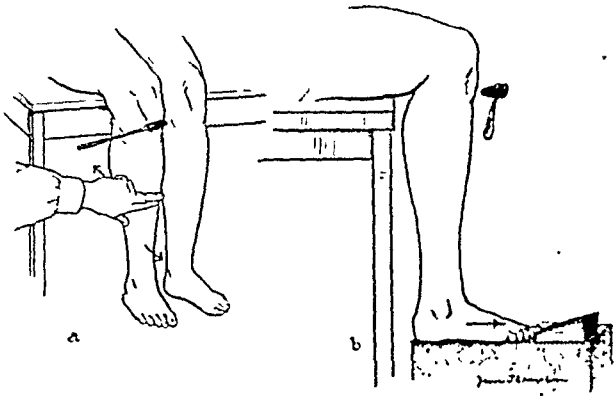
Fig. 1.—Method of reenforcement of the patellar reflex by active innervation of the quadriceps muscle. (a) The patient pushes his leg slightly forward; the examiner opposes this movement with his left hand and simultaneously strikes the patellar tendon with the hammer held in the right hand. (b) The patellar tendon is struck by the examiner while the patient pushes his foot against resistance offered by the perpendicular surface of the block on the footstool.

Sträussler[56] stated that he tapped the patellar tendon immediately after a brisk, passive bending at the knee. This maneuver increases the innervation of the quadriceps muscle, increases its tension and thus facilitates the elicitation of the patellar reflex.

From all these observations an important and workable maneuver for the reenforcement of the deep reflexes results. When a reflex is being elicited, a slight voluntary contraction of the muscles involved in this reflex must take place. The invisible reflex may then become visible and the weak one appear stronger. The practical procedure for facilitation of the appearance of the patellar reflex, for instance, is as follows: The patient sits on a table, his legs hanging loosely; he is asked to push one foot slightly forward against the resistance of the fingers of the examiner, who thus can appraise and control the amount of pressure exerted by the patient. This control is important because the innervation of the quadriceps muscle must be very slight. A strong effort on the part of the patient may not facilitate the elicitation of the reflex; on the

contrary, it may interfere with its appearance. The moment the patient innervates the quadriceps muscle, the patellar tendon is tapped and the reflex elicited (fig. 1 a). Another method is to ask the patient, while sitting on the table with his feet resting flat on the footstool, to push his foot slightly against the perpendicular surface of the block which extends across the footstool (fig. 1 b). For elicitation of the achilles reflex, the patient is asked to push the ball of his foot slightly downward, so that the calf muscles are innervated; the examiner opposes this movement with his hand and so controls the pressure exerted by the patient. The achilles tendon is tapped the moment the patient presses his foot down (fig. 2 a). Or the patient, sitting on the table, with his foot resting on the footstool and the ball of the foot placed on the angular surface of a block on the footstool, is asked to push the ball of his foot down slightly (fig. 2 b). Similar procedures may be used for elicitation of other reflexes. The effect of a slight, active flexion of the fingers on the reenforcement or appearance of the finger flexor reflex is particularly striking. In my experience the method of increased innervation has undoubtedly been the best means of elicitation and reenforcement of the deep reflexes. No deep reflexes should be declared as lost unless this method has been tried (Roemheld[57]).
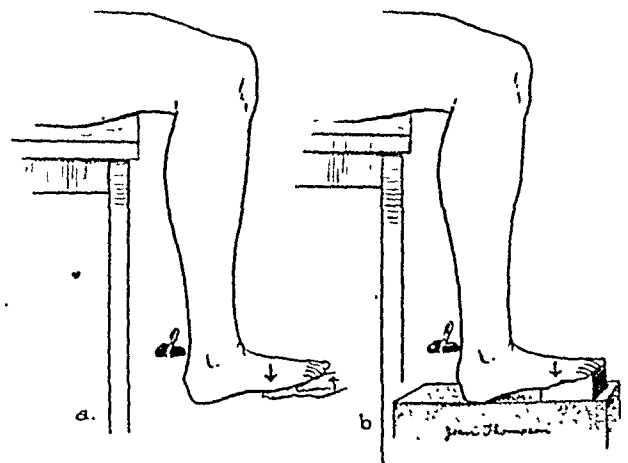
Fig. 2.—Method of reenforcement of the achilles reflex. (a) The patient, sitting on the table with the legs hanging loosely, pushes down the ball of the foot slightly against the hand of the examiner while the latter strikes the achilles tendon with the hammer. (b) The achilles tendon is struck by the examiner while the patient presses the ball of the foot against the angular surface of the block on the footstool.

I shall now consider individually some of the clinically most important reflexes.

55. Jacobson, E., and Carlson, A.: The Influence of Relaxation upon the Knee-Jerk, Am. J. Physiol. **73:** 324, 1925.

56. Sträussler, E.: Ein einfacher Kunstgriff zur Auslösung schwer auslösbarer Patellarreflexe, Wien. med. Wchnschr. **82:**398, 1932.

57. Roemheld, L.: Ueber die Auslösung der Eigenreflexe und ihre Bedeutung, Deutsche med. Wchnschr. **64:**46, 1938.

ORBICULARIS OCULI REFLEX

The orbicularis oculi muscle protects by contraction the bulbus oculi and the retina from external noxious influences. The mechanism of its reflex action is especially elaborate and shows peculiarities which other muscles do not possess. The threshold for reflexive contraction is extremely low. The reaction of the muscle is rapid—so rapid that in every language there is the expression "quick as a wink." The reaction is bilateral. A further outstanding characteristic of the reflex mechanism of this muscle is the great variety of stimuli which bring it into play. The orbicularis oculi muscle contracts reflexly on stimulation of the cochlea, the phenomenon being known as the cochleopalpebral reflex, or the auropalpebral or acousticopalpebral reflex. This reaction is strikingly manifested when the patient is startled by an unexpected sound, such as a pistol shot (Strauss, Landis and Hunt[58]). The muscle contracts also on visual stimuli, when an object or light is suddenly brought into the field of vision; this is the old visual orbicularis reflex of Descartes, also called the wink reflex, or the opticofacial reflex (Borowsky[59]).

Imperatori[60] recently described a palato-palpebral reflex, in which the eye closes when the palate is touched. Gallenga[61] observed in dogs, either normal or decerebrated, a reflex contraction of the orbicularis oculi muscle on stimulation of the superior laryngeal nerve. The extreme delicacy and responsiveness of the highly efficient reflex mechanism of the orbicularis oculi muscle may be demonstrated in other ways (Galant[62]). It may be compared with the cough reflex. This, too, may be elicited in many ways. The orbicularis oculi muscle has its skin-muscle reflex—the corneal reflex may be regarded as such. One may assume that this muscle has also its own muscle reflex, which is evoked by direct concussion and stretching of the muscle substance. This response, which should be called the orbicularis oculi reflex, can be elicited by tapping the muscle directly or by tapping the neighboring bones—the front of the head, the temporal area or the bone and cartilages of the nose. Since, as has been seen,

the threshold of a reflex contraction of the orbicularis oculi muscle is extremely low, it is understandable that the slightest concussion of the bone on the surface of which the muscle directly lies may, by transmission of the concussion to the muscle, evoke its contraction. The fibers of the orbicularis oculi muscles are intimately interwoven with each other and with the surrounding muscles of the face. They represent an anatomic continuity which makes them a physiologic unity. Thus, the slightest concussion of the neighboring muscles is easily transmitted to the homolateral and to the heterolateral orbicularis oculi muscle. Weisenburg[63] stated:

The normal reflex [of the orbicularis oculi muscle] is obtained by tapping over the frontal region as far as the border of the hair, the exaggerated form by tapping as far back as the vertex, and the diminished form can only be obtained by tapping directly over the supra-orbital nerve.

With this one may agree, except that it is the tapping of the muscle or the bone, and not the supraorbital nerve, that constitutes the essential stimulus. The nearer the point of stimulation is to the muscle, the stronger is the reflex.

The orbicularis oculi muscle, especially its lower part, reacts so easily to such a multitude of external stimuli that on tapping either this muscle or its neighboring area one runs the danger of eliciting a reflex of a different order, of affecting the muscle through means other than concussion and stretching. Care must be taken to avoid as far as possible these other stimuli. It is of course impossible to avoid them completely. With careful technic, however, one has a definite impression that the element of direct concussion and stretching of the muscles in elicitation of the reflex is so dominant that, whereas other stimuli are capable of producing the reflex, they do not enter into practical consideration.

By the following technic (fig. 3), for instance, one avoids to a maximal degree every stimulus other than stretching, i. e., visual or auditory stimuli, startling, gross irritation of the skin in any form and stimuli to the periosteum or bone. The examiner holds a fold of skin between his thumb and index finger at the outer corner of the eye, at the temple, pulling it slightly backward so as to stretch the orbicularis oculi muscle mildly. The examiner then taps his thumb lightly with the reflex hammer, or with a finger of the other hand, and evokes a sudden additional stretching of the muscle. A reflex contraction of the orbicularis oculi muscle follows on this side and, to a milder degree, on the other

58. Strauss, H.; Landis, C., and Hunt, W. A.: Acoustic Motor Reactions, Arch. Otolaryng. **28**:941 (Dec.) 1938.

59. Borowsky, M. L.: Der Blinzelabwehrreflex, usw., Deutsche Ztschr. f. Nervenh. **110**:134, 1929.

60. Imperatori, C. J.: The Palatal Palpebral Reflex, M. J. & Rec. **131**:198, 1930.

61. Gallenga, R.: Sopra un riflesso palpebrale, Ateneo parmense **1**:585, 1929.

62. Galant, J. S.: Die Lidreflexe, Arch. f. Kinderh. **74**:130, 1924; Die Blinzelreflexe und einige andere Lidphänomene, ibid. **75**:37, 1925.

63. Weisenburg, T. H.: A Consideration of the Facial Reflexes and Nerve and Muscle Phenomena in the Distribution of the Fifth and Seventh Nerves, Univ. Pennsylvania M. Bull. **16**:63, 1903-1904.

side, exactly in proportion to the strength of the tapping. Here it is evident that the orbicularis oculi muscle contracts reflexly, as is the case with all other muscles on sudden passive stretching of the muscle fibers themselves. The response, then, is a true deep muscle reflex, a muscle-muscle reflex. The assumption that the orbicularis oculi muscle has a deep muscle reflex of its own is based on purely clinical observation. To this opinion I adhere, despite the fact that Sommer,[64] a pupil of Hoffmann, on examination of the electric currents of the muscle, concluded that the mimic muscles of the face have no deep reflexes, no *Eigenreflexe,* according to the terminology of Hoffmann. Long before him, Sternberg[8] asserted that no "tendon reflexes" existed in the facial muscles.

The reflex appearing on concussion and stretching of the orbicularis oculi muscle is a normal phenomenon, and its strength varies
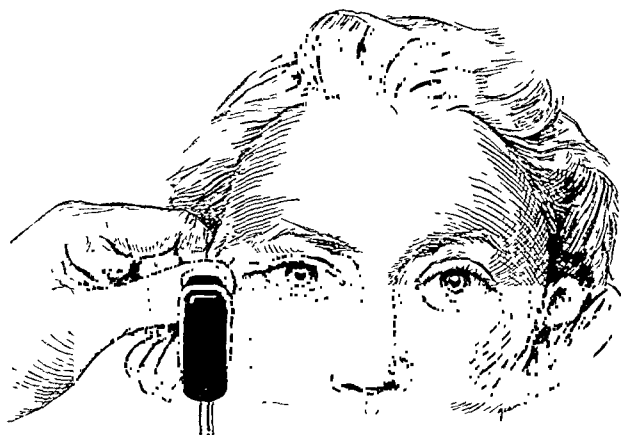
Fig. 3.—Method of elicitation of the orbicularis oculi reflex. The examiner holds a fold of skin over the temple between his thumb and index finger; he pulls slightly backward and strikes his thumb lightly with the hammer or his finger, thus causing additional stretching of the orbicularis oculi muscle.

greatly in different persons, as is the case with every other deep muscle reflex. One cannot subscribe to Foerster's[65] statement that this reflex is inconstant. Its constancy was emphasized in special studies of Zeri,[66] Kartschikjan[67] and Weingrow.[68] Weingrow called it "a true

and absolutely constant reflex," and with him I agree. The reflex is also constant in apes (Aronovitch[69]). The greatest diagnostic importance of this reflex lies in the fact that its diminution indicates a facial palsy of peripheral type and that the degree of this diminution parallels that of the palsy. In a case of facial palsy of central type the reflex is either preserved or exaggerated (Bickel[70] and Glattauer[71]). Of physiologic interest is the exaggeration of this reflex in cases of postencephalitic parkinsonism (Zylberlast-Zand;[72] Guillain, Alajouanine and Marquézy[73]). This exaggeration is so constant that it must be regarded as a definite sign of parkinsonism.

This reflex is usually classified as a superficial, or cutaneous, reflex. Overend[74] expressed the opinion that it was "a true skin reflex and not a periosteal reaction." Von Bechterew,[75] Foerster[76] and Monrad-Krohn[77] saw in it a periosteal reflex. Guillain[78] called it a cutaneous and periosteal reflex. Simchowicz[79] spoke of a perichondrial reflex which may be transformed into a periosteal one. Lewandowsky[80] called it a bone reflex. Kornilow[81] expressed the belief that this reflex was neither cutaneous nor periosteal, but that it belonged to the "defense reflexes." Böhme[82] saw in it a protective reflex

64. Sommer, J.: Hat die mimische Gesichtsmuskulatur Eigenreflexe oder nicht? Deutsche Ztschr. f. Nervenh. **146:**294, 1938.

65. Foerster, O., in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1936, vol. 6, p. 238.

66. Zeri, A.: Du réflexe trigémino-facial ou trigéminoorbiculaire des paupières, Ann. d. Ist. sichiat. d. r. Univ. di Roma **3:**269, 1904; abstracted, Rev. neurol. **14:**15, 1906.

67. Kartschikjan, S.: Motor Reaction of the Face Muscles on Mechanical Stimulation, Obozr. psikhiat., nevrol. **2:**175, 1922.

68. Weingrow, S. M.: Facial Reflexes, Arch. Pediat. **50:**234, 1933.

69. Aronovitch, G. D.: Reflexes in Apes, J. Nerv. & Ment. Dis. **65:**457, 1927.

70. Bickel, A.: Die klinische Bedeutung der Knochenreflexe, Charité-Ann. **36:**186, 1912.

71. Glattauer, A.: Zur Physiopathologie und Klinik des Nasenrückenlidreflexes, Schweiz. Arch. f. Neurol. u. Psychiat. **44:**243, 1939.

72. Zylberlast-Zand, N.: Le réflexe oculo-palpébral chez les parkinsoniens postencéphalitiques, Rev. neurol. **39:**102, 1923.

73. Guillain, G.; Alajouanine, T., and Marquézy, R.: L'exagération du réflexe naso-palpébral dans les syndromes post-éncephalitiques, Compt. rend. Soc. de biol. **91:**364, 1924.

74. Overend, W.: Preliminary Note on a New Cranial Reflex, Lancet **1:**619, 1896.

75. von Bechterew, W.: Ueber Reflexe im Antlitz- und Kopfgebiete, Neurol. Centralbl. **20:**930, 1901.

76. Foerster,[65] p. 239.

77. Monrad-Krohn, G. H.: The Clinical Examination of the Nervous System, ed. 7, New York, Harper & Bros., 1938, p. 126.

78. Guillain, G.: Le réflexe naso-palpébral (réflexe trijumeau-facial) et sa valeur pronostique dans la paralysie faciale, Compt. rend. Soc. de biol. **83:**1394, 1920.

79. Simchowicz, T.: Ueber den Nasenaugenreflex und den Nasenkinnreflex, Deutsche Ztschr. f. Nervenh. **75:**343, 1922.

80. Lewandowsky, M., in Handbuch der Neurologie, Berlin, Julius Springer, 1910, vol. 1, p. 584.

81. Kornilow, A.: Ueber cerebrale und spinale Reflexe, Deutsche Ztschr. f. Nervenh. **23:**216, 1903.

82. Böhme, A., in Bethe, A.; Bergmann, G., and others: Handbuch der normalen und pathologischen Physiologie, Berlin, Julius Springer, 1927, vol. 10, p. 982.

of the eye. Moro[83] observed that this reflex was constant in the newborn and in infants on tapping of the forehead, and occasionally the dorsum or the tip of the nose. This reflex did not appear on the tapping of other points. This speaks, according to Moro, against the simple protective nature of the reflex. My view of the nature of this important reflex may be summarized as follows: The threshold for reflex action of the orbicularis oculi muscle is extremely low. Its contraction may be effected, as has been seen, through multitudinous stimuli, and application of a single stimulus is certainly difficult. Nevertheless, with careful technic one has a definite impression that other stimuli are reduced to a minimum and that concussion and stretching alone are effective. It is therefore justifiable to assume that the orbicularis oculi muscle has its own deep muscle reflex, as have all other muscles. It is the painstaking observation on the technic of elicitation that teaches one unmistakably the nature of this reflex, that of a true muscle stretch reflex.

This reflex has a long history. It was first described by Overend[74] in 1896 as "a new cranial reflex," or "frontal reflex." He elicited the phenomenon by gently tapping the forehead. He also noticed that a tap on the middle line of the forehead was followed by twitchings on both sides. This reflex is usually named after McCarthy,[84] who in 1901 described it as a "supraorbital reflex." He attributed what he called "fibrillary tremor, but not contraction," of the orbicularis oculi muscle to the tapping of the supraorbital nerve. Under the name "ocular reflex," von Bechterew[85] described the same phenomenon: contraction of the orbicularis oculi muscle when any point over the frontotemporal or zygomatic area of the skull was tapped. In disagreement with McCarthy, he emphasized that one is dealing here with a contraction of the muscle and that this can be achieved in other ways than by taping the supraorbital nerve. Weisenburg,[63] in 1903 spoke of "the ophthalmic, or supra-orbital, reflex." In 1904 this reflex was again described by Zeri[66] as the trigeminofacial, or the trigemino-orbicular, reflex, and in 1907 it

was described by Mondino.[86] In 1920 Guillain[78] described a "nasopalpebral reflex," which was elicited by percussion at the root of the nose. This is not a "variant" of the McCarthy reflex, as it is often called, but is the same reflex. Eighteen years before Guillain, von Bechterew[85a] stressed that this reflex can be elicited over the whole area of the frontal muscle. Since the value of this reflex lies essentially in the comparative strength of the contractions of the orbicularis oculi muscle on the two sides, the most practical point of elicitation is the glabella; however, there is no use in proposing a new name, "glabella reflex," as I[87] did in 1930. Physiologically and didactically it is more correct to name the reflex according to the muscle involved than according to the point of its elicitation. In 1922 Simchowicz[79] described the same reflex under the name "nose-eye reflex." He elicited this reflex by tapping the tip of the nose, as Moro[83] had done long before him. In some cases he found a very weak, hardly perceptible contraction of the lower lid. It is easily understandable that when the nose is tapped the provoked concussion of the underlying cartilage and bones can be transmitted to the orbicularis oculi muscles, the threshold of stimulation of which is very low. Simchowicz expressed the opinion that the reflexes of von Bechterew, McCarthy and Zeri are "closely related." They are, in fact, completely identical. According to Simchowicz, his reflex is "the first example of a perichondrial reflex." He interpreted the fact that the reflex can be elicited not only from the bridge of the nose as far as the glabella but from the frontal bone as "a transformation of a perichondrial reflex into a periosteal." Glattauer,[71] too, spoke of a periosteal-perichondrial reflex. But there is as little evidence of the existence of perichondrial as of periosteal reflexes. It is more logical to assume that every concussion of neighboring structures, whether of the nose or of the frontal bone, is easily transmitted to the orbicularis oculi muscles, where it readily provokes a contraction.

In a search for new reflexes, Galant,[88] in 1926, described a "cephalopalpebral reflex" consisting of contraction of the orbicularis oculi muscle, chiefly of the lower lid, when the top of the skull

83. Moro, E.: Ueber Gesichtsreflexe bei Säuglingen, Wien. klin. Wchnschr. **19**:637, 1906.

84. McCarthy, D. J.: Der Supraorbitalreflex, Neurol. Centralbl. **20**:800, 1901; Weiteres zur Kenntnis des Supraorbitalreflexes, ibid. **21**:843, 1902.

85. von Bechterew, W.: (a) Ueber den Augenreflex oder das Augenphänomen, Neurol. Centralbl. **21**:107, 1902; (b) Ueber den Zustand der Muskel- und sonstigen Reflexe des Antlitzes bei Dementia paralytica, ibid. **22**:850, 1903; (c) footnote 75.

86. Mondino, C.: Di uno speciale riflesso che si osserva nella contrattura facciale, Riv. di pat. nerv. **12**:49, 1907; abstracted, Neurol. Centralbl. **26**:855, 1907.

87. Wartenberg, R.: Kleine Hilfsmittel der neurologischen Diagnostik, Nervenarzt **3**:594, 1930.

88. Galant, J. S.: Der cephalopalpebrale Reflex (CPR), der cephalopalpebro-nasale Reflex (CPNR) und ihnen verwandte Reflexe, die vom schädeldach ausgelöst werden, Psychiat.-neurol. Wchnschr. **28**:490, 1926.

is tapped. He elicited this reflex in persons with neuroses of many kinds. This new term has no right to existence, since the reflex is apparently only an orbicularis oculi reflex elicited by concussion of the frontal bone. Here the reflex is elicited from a slightly more distant point. Elicitation of this response is possible in persons with increased general reflex irritability, which includes the normally extremely susceptible orbicularis oculi muscle. It is possible that this reflex is a startle action, the threshold of which is very low in neurotic persons. The latest publication on this subject appeared in 1939, in which Glattauer[71] recommended the name "nose-bridge-lid reflex."

The chaos of nomenclature concerned with this reflex is best illustrated by the following statement in a paper published in 1937, describing the neurologic status in a case: "supraorbital, nasopalpebral, glabella reflexes preserved." These three names, like all others—for instance, nose-bone reflex, eye closure reflex, eye reflex, nose-eye reflex, trigeminofacial reflex and trigemino-orbicular reflex—should be replaced by the simple, physiologically correct name "orbicularis oculi reflex." It is the muscle, not the bones, the skin, the periosteum or the perichondrium, which is at the root of this phenomenon.

JAW REFLEX

When the muscles which elevate the lower jaw and close the mouth are subjected to a brisk stretching, they contract and the lower jaw moves briskly upward. This constitutes the jaw reflex, usually called the masseter reflex. This name is not quite correct, since in closing the mouth, not only the masseter but the temporal muscles are involved. Although mentioned by Fuller[89] in 1884, this reflex was first described in 1886 by de Watteville[90] who called it the jaw jerk, or the masseteric tendon reaction. Von Bechterew[75] called it the mandibular reflex.[29] Since this reflex is practically the only one concerned with the jaw, it is appropriately called the jaw reflex, as Dana[91] did. The sudden stretching of the muscles which close the mouth may be accomplished in various ways. The front of the chin may be tapped directly with the reflex hammer; the thumb may be placed on the chin and tapped, or a tongue blade may be placed on the lower teeth and tapped. Jendras-

sik[92] could elicit this reflex easily, also, by tapping the lower surface of the zygomatic arch at the point of insertion of the masseter muscle. As was pointed out previously,[93] this reflex can easily be elicited also by tapping a tongue blade placed on the root of the tongue, without touching the teeth. The exaggeration of the reflex is more conspicuous, and the reflex appears on milder stimuli, with this technic than with direct tapping of the lower jaw. This reflex may be increased, even to a state of clonus of the lower jaw, in cases of bilateral suprapontile cerebral lesions, for instance pseudobulbar palsy.[94] This association was first described by Beevor.[95] It is worthy of note that the jaw reflex may be exaggerated without proper "pseudoparalytic" signs, the localization of the lesion being the decisive factor. The clinical value of this reflex is generally slight. Curschmann[96] pointed out that the behavior of the jaw reflex may be of value in the differential diagnosis of hyporeflexia and areflexia on a constitutional basis or on the basis of a local lesion. If not only the reflexes of the muscles of the limbs but the jaw reflex is absent, the areflexia is probably constitutional. If the jaw reflex is preserved and the reflexes of the limbs are lost, a local pathologic process is probably at work.

HEAD RETRACTION REFLEX

The muscles of the back of the neck, the retractors of the head, have a deep muscle reflex of their own. This reflex was described in detail in a previous paper (Wartenberg[97]). To elicit this reflex one evokes a quick, sharp bending of the head. This is best achieved by sharply tapping the maxillary bone beneath the nose while the head is slightly bent. If a brisk, quick, involuntary backward jerk of the head takes place, the reflex is said to be positive. If only a slight concussion of the whole head results from the tap, the reflex is absent. This reflex

89. Fuller, S. E.: Pseudo-Bulbar Paralysis, M. Rec. 26:487, 1884.

90. de Watteville, A.: Note, Brain 8:518, 1886.

91. Dana, C. L.: Text-Book of Nervous Diseases, ed. 10, Baltimore, William Wood & Company, 1925, p. 57.

92. Jendrassik, E.: Ueber die allgemeine Localisation der Reflexe, Deutsches Arch. f. klin. Med. 52:574, 1894.

93. Wartenberg, R.: Zur Klinik und Pathogenese der Pseudobulbärparalyse, Monatschr. f. Psychiat. u. Neurol. 51:251, 1922.

94. The textbooks use the time-honored, but misleading, term "pseudobulbar palsy." To distinguish the two types of bulbar palsy, the nuclear and the supra-nuclear, the term "flaccid bulbar palsy" and "spastic bulbar palsy" are preferable.

95. Beevor, C. E.: A Case of Amyotrophic Lateral Sclerosis with Clonus of the Lower Jaw, Brain 8:516, 1886.

96. Curschmann, H.: Ueber konstitutionelle Hypo- und Areflexie, Deutsche Ztschr. f. Nervenh. 83:51, 1925.

97. Wartenberg, R.: Head Retraction Reflex, Am. J. M. Sc. 201:553, 1941.

is usually not observed in normal persons but can be seen distinctly in patients with bilateral lesions of the pyramidal tracts which involve the nuclei of innervation of retractor muscles of the head. Though the evaluation of this reflex is sometimes difficult, a critical review of my own experience convinced me that this reflex may be of great, sometimes of decisive, help in the diagnosis of bilateral supracervical lesions of the pyramidal tract. The reflex is most clearly seen in cases of advanced amyotrophic lateral sclerosis, bilateral spastic paralysis and dorsolateral sclerosis.

FINGER FLEXOR REFLEX

The flexors of the fingers react like any other striated muscle: They contract on brisk stretch. This contraction constitutes the finger flexor reflex. There are numerous ways in which one may effect a sudden stretching of the finger flexors which will result in their contraction. The best method is as follows (fig. 4): The patient, his half-supinated hand resting with its dorsum on his knee, sits facing the examiner. The examiner places his middle and index fingers across the slightly bent tips of the patient's four fingers and taps his own fingers lightly with the percussion hammer. A flexion of the patient's four fingers, as well as of the end phalanx of the thumb, is felt and seen. This response constitutes the positive reflex. It is essential that the hand of the examiner be loose and that the blows of the hammer be dealt swiftly, briskly, abruptly and with maximal elasticity. . The fingers should not be palpated, but should be struck suddenly.

The best method of reenforcing this reflex, that is, of making it appear at all if it is not perceptible or of making it more distinct, is to have the patient bend his fingers when the blow is applied. This method is effective and is highly recommended. It is essential of course that the active bending of the patient's fingers be slight. While many authors, for instance Perelman,[98] have stressed the importance of complete relaxation of the fingers on examination for Hoffmann's sign, I contend that the optimum position for this examination is a slight, active bending of the fingers.

It is often necessary to repeat the examination, and with varying force, while the patient's fingers are bent in different degrees and while the position of the hand is slightly changed. The direction of the blow of the percussion hammer may be modified, too. The reflex is "whimsical." The results of repeated tests may differ. By careful application of the aforementioned technic,

by patient repetition of the examination and by delicate use of the method of reenforcement, one can elicit this reflex in normal persons in full, with flexion of all the fingers and of the thumb.

The finger flexor reflex must thus be regarded as a normal reflex. Of course its palpable, visible evidence varies greatly, as is true of many other reflexes. It is sometimes barely perceptible and often greatly diminished. It is occasionally elicited only through the method of reenforcement described. This is simply because, as Moore[99] pointed out, the normal tonus of the finger flexors varies notably in different persons. It must be stressed that the presence of the reflex does not constitute a sign of a lesion of the pyramidal tract. With such a
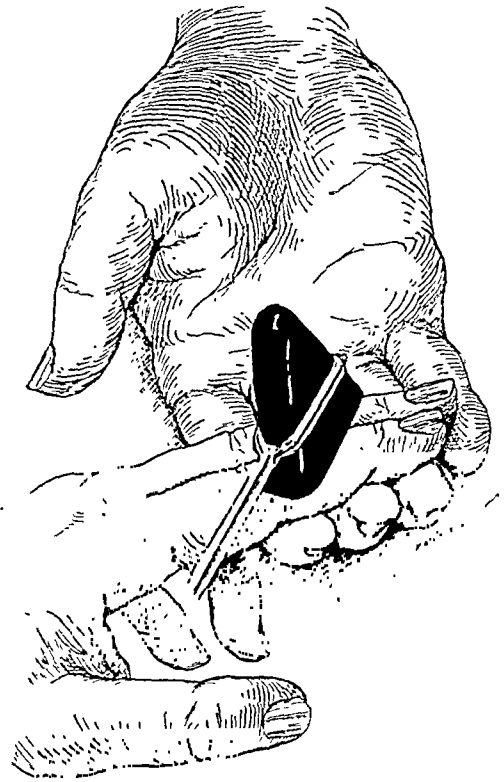
Fig. 4.—Method of elicitation of the finger flexor reflex. The patient bends the terminal phalanges of his fingers; the examiner places his middle and index fingers on the volar surface of the phalanges and strikes his own fingers with the hammer; reflex contraction of the patient's fingers can be seen and felt.

lesion this reflex is distinct, but the reverse is not true: A greatly increased reflex does not in itself indicate a lesion of the pyramidal tract. In other words, a patient with a strongly positive finger flexor reflex *may* have a pyramidal lesion, but not necessarily. If this reflex is strongly positive or is exaggerated, one may, it is true, suspect the presence of a pyramidal lesion, but there is no definite way by which one may distinguish exaggeration of the finger flexor reflex due to functional hyperirritability and that due to a lesion of the pyramidal tract. The same

98. Perelman, I.: The Sign of Hoffmann and Its Clinical Importance, Sovet. nevropat. **4**:145, 1935.

99. Moore, R.: Reflex of the Upper Extremity, J. A. M. A. **65**:528 (Aug. 7) 1915.

is true of other reflexes, such as the patellar. That the finger flexor reflex may be barely perceptible in normal persons, or not perceptible at all, does not mean that when it is distinct it is indicative of a lesion of the pyramidal tract. Like many other reflexes, this reflex often exists in latent form.

This reflex, consisting of flexion of the fingers on tapping of their volar tips, is often called the "finger Rossolimo" sign. Foerster [100] called the "finger Rossolimo" sign, together with the Babinski and the "toe Rossolimo" sign, the fine diagnostic signs of a lesion of the pyramidal tract. Although this statement was made by no less a man than Foerster, one cannot subscribe completely to the assertion in this form, since it is misleading. The finger Rossolimo sign is in itself not a pyramidal sign. It may be considered pathologic only when it is highly exaggerated or appears unilaterally.

There are many ways by which one may stretch the flexor muscles of the fingers and elicit the finger flexor reflex. About 1900 Hoffmann introduced a method of elicitation of the reflex which has been known as Hoffmann's sign, Hoffmann's "reflex phenomenon," the "snapping reflex" or the "digital reflex." He never described the reflex; this was first done in 1911 by his pupil Curschmann.[101] This sign, interestingly, has a greater popularity in America than in Europe, or even in Germany. Several articles devoted to this sign have been published in the United States (Keyser,[102] Pitfield,[103] Fay and Gotten [104] and Echols [105]). Even a history of the Hoffmann sign has been written (Bendheim [106]). The technic of elicitation of this reflex is as follows: The examiner holds the middle phalanx of the patient's middle finger between his own second and third fingers and, with a sharp and forcible flick of his thumb, nips the nail of the patient's finger, thus flexing it and suddenly releasing it. The reflex is said to be positive when flexion of the other fingers, including the thumb, follows.

There is little in the literature on the physiology of this phenomenon. Close examination of the technic of its elicitation makes it clear that it is based on the same stretching of the finger flexors as that in the finger flexor reflex, already described. The sudden, forcible, passive flexion of the end phalanx of the middle finger is followed by a sudden release, which consists of sudden stretching of the flexor muscle of the third finger with subsequent reflexive bending. The stretching of one flexor muscle mechancially involves the other flexors as well. The Hoffmann reflex represents thus only a special technic of elicitation of the previously discussed finger flexor reflex. It is of course easier to provoke a sudden stretching by application of a direct blow to the volar surface of the finger tips than by use of the method of Hoffmann. Therefore Hoffmann's technic of elicitation is cruder than the method previously described. Hence it often occurs that the finger flexor reflex is elicited by the method described here while it is not obtained by Hoffmann's method.

In numerous textbooks and articles Hoffmann's reflex has been designated as a pyramidal sign, "equally as valuable as a Babinski sign." Grinker [107] asserted, to cite one of the latest statements, that on elicitation of the Hoffmann reflex the resultant movement is a flexion of the terminal phalanx when a lesion of the pyramidal tract exists. Purves-Stewart [108] said: "In health, the patient's thumb remains motionless, but in disease of the pyramidal fibers of the upper limb the thumb makes a quick reflex movement of flexion and adduction." In my opinion, to Hoffmann's sign applies all that has been said of the finger flexor reflex, since the two are based on the same mechanism and are therefore identical. It is essential to stress that however valuable a pyramidal sign the Hoffmann reflex may be, it is not in itself pathologic; it indicates, if outspoken, only a state of increased muscular tonus, which may be pyramidal, but may also be purely functional, and therefore is diagnostically insignificant. The Hoffmann reflex is so obviously a muscle stretch reflex, as are the finger flexor reflex and all the so-called tendon reflexes, that it is hardly necessary to criticize the view of Keyser [102] who stated that ". . . the Hoffmann reflex belongs to the group of defense movements, in contradistinction to the tendon reflexes."

It is interesting to note that despite the countless declarations that the Hoffmann sign is

100. Foerster,[65] p. 244.

101. Curschmann, H.: Ueber die diagnostische Bedeutung des Babinskischen Phänomens im präurämischen Zustand, München. med. Wchnschr. **58:**2054, 1911.

102. Keyser, T. S.: Hoffmann's Sign or the "Digital Reflex," J. Nerv. & Ment. Dis. **44:**51, 1916.

103. Pitfield, R. L.: The Hoffmann Reflex: A Simple Way of Reinforcing It and Other Reflexes, J. Nerv. & Ment. Dis. **69:**252, 1929.

104. Ray, T., and Gotten, H.: Clinical Observations on the Value of the Hoffmann Sign, J. Nev. & Ment. Dis. **77:**594, 1933.

105. Echols, D.: The Hoffmann Sign, J. Nerv. & Ment. Dis. **84:**427, 1936.

106. Bendheim, O. L.: On the History of Hoffmann's Sign, Bull. Inst. Hist. Med. **5:**684, 1937.

107. Grinker,[39] p. 260.

108. Purves-Stewart, J.: The Diagnosis of Nervous Diseases, ed. 8, Baltimore, William Wood & Company, 1937, p. 540.

indicative of a lesion of the pyramidal tract, one finds in the literature numerous, scattered critical comments and observations which cast doubt on the value of this sign as an indication of a pyramidal lesion. Dana [91] stated: "Its presence generally indicates a pyramidal tract lesion, but it is not very trustworthy." Echols [105] was cautious enough to declare that "Hoffmann's sign almost always indicates a disturbance of the pyramidal pathways." He said "almost" rightly, since he elicited an unexplained Hoffmann sign in 1.63 per cent of male university students. Pitfield [103] stated, with some resignation, that the Hoffmann sign ". . . is confusingly present in ephemeral and functional disorders. It is a sign of disease or of some dysfunction of the body." Keyser [102] found a positive Hoffmann sign ". . . also in some functional cases associated with 'lively, deep reflexes.' " Perelman [98] noted some exceptions to the rule that Hoffmann's sign is positive only in the presence of organic lesions—exceptions that in his opinion needed further investigation. An opinion regarding the nature of the Hoffmann reflex most in accord with that expressed in this paper was stated by Brain [109]: ". . . The Hoffmann is probably an index of muscular hypertonia rather than of a pyramidal lesion as such. . . . It may be elicitable in a nervous individual with no organic disease." The word "probably" should be omitted, and the term "muscular hypertonia" is not quite correct, since the degree of muscle tonus necessary for the appearance of the Hoffmann sign lies completely within normal limits.

In 1912 Trömner [110] described a finger reflex which carries his name. He called it the finger phenomenon. The patient keeps his fingers flexed, and the examiner taps with his own middle finger the volar surfaces of the tip of the middle or the index finger of the patient. A flexion of all the fingers, including the thumb, constitutes a positive reflex. Weisz [111] observed that in cases of organic disturbance the Trömner reflex is positive when the arms become spastic and increases with the increase in spasticity; however, it may be absent when the spasticity is severe and contracture develops. It is absent in cases of fresh pyramidal lesions—for instance, in cases of apoplexy. It is obvious that this response is a finger flexor reflex elicited by stretching of the flexors of the middle or the

middle and the index finger. The appearance and the degree of strength of this reflex depend on the tonus of the muscles and on the amount of brisk stretching to which the muscles have been subjected. This reflex may be distinct with pyramidal lesions, but by no means appears with these alone. To the Trömner reflex applies what has already been said about the finger flexor reflex. It is misleading, even wrong, to speak of the Trömner reflex as a pyramidal sign. Trömner,[110] in 1912, said that his reflex was analogous to the Babinski sign and was as pathognomonic for the arm as the Babinski sign is for the leg. In 1913 Trömner [112] asserted that he found this reflex always, and only, in cases of spastic paralysis of the arm. But ten years later, in 1923, he [113] confessed that in eliciting his phenomenon, "one may see mild flexion of the fingers with neuropathic conditions as well, but that stronger reactions indicate a pyramidal lesion." This, in essence, is practically a renunciation of the idea that the Trömner reflex is pathognomonic of a pyramidal lesion. It is of course impossible to ascertain in a given case when the Trömner reflex should be regarded as due to a lesion of the pyramidal tract and when to a functional disturbance. No such distinction can be made, since the Trömner reflex, though often latent, is a normal reflex and when strongly positive is only a pathologic exaggeration of a basically normal reflex.

Yet, in the last edition of his classic textbook, Sahli [114] spoke of a "Trömner finger phenomenon associated with a pyramidal lesion." Böhme [115] stated in his monograph on reflexes: "The Trömner reflex is to be regarded as analogous to the Rossolimo toe reflex and speaks diagnostically for a lesion of the pyramidal tract." Pool [116] listed the Hoffmann and the Trömner sign as reflexes ". . . due to central pyramidal tract lesions." In the last edition of his textbook, Bing [117] listed the reflex of Trömner among the pathologic reflexes associated with the spastic syndrome.

According to the view expressed in this paper, the Trömner reflex represents nothing more

109. Brain, R.: Diseases of the Nervous System, ed. 2, London, Oxford University Press, 1940, p. 45..

110. Trömner, E.: Fingerbeugephänomen, Neurol. Centralbl. **31**:603, 1912.

111. Weisz, S.: Ueber Pyramidenzeichen am Arm, Nervenarzt **6**:179, 1933.

112. Trömner, E.: Ueber Sehnen-resp. Muskelreflexe und die Merkmale ihrer Schwächung und Steigerung, Berl. klin. Wchnschr. **50**:1712, 1913.

113. Trömner, E.: Zur Technik der Reflexprüfung, Klin. Wchnschr. **2**:1810, 1923.

114. Sahli, H.: Lehrbuch der klinischen Untersuchungsmethoden, ed. 7, Leipzig, Franz Deuticke, 1932, vol. 3, p. 225.

115. Böhme,[82] p. 973.

116. Pool, J. L.: Manual Reflex, Bull. Neurol. Inst. New York **6**:372, 1937.

117. Bing, R.: Lehrbuch der Nervenkrankheiten, ed. 6, Berlin, Urban & Schwarzenberg, 1940, p. 167.

than a method for bringing about sudden stretching of the finger flexors necessary for elicitation of the finger flexor reflex—and not the best method. The method described previously, that of placing the examiner's index and middle fingers across the four, slightly bent fingers of the patient and then tapping his own fingers briskly, abruptly and sharply, is by far more efficacious. It is all the more so when one combines this technic with the method of re-enforcement by asking the patient to bend his fingers slightly. By using both these methods one can elicit the finger flexor reflex more easily than by any other method, and one sees this reflex so commonly that it cannot be regarded as pathologic. The finger Rossolimo sign, as this finger flexor reflex is often termed, is not a mysterious, "primitive" sign, as Voss[118] called it, that must be explained phylogenetically; it is an ordinary reflex, such as can be elicited from any other muscle of the human body, with the only distinction that it exists in more latent form than some other muscle stretch reflexes.

This concept is the same as that of Cooper,[119] who suggested that the Trömner reflex ". . . may be the response to stretching of the flexor muscles or their tendons when a state of abnormally increased muscle tonus or abnormally lowered resistance of the threshold of reflex excitability exists" and that ". . . it is a tendon reflex rather than purely a defense withdrawal effect." I should go a step further and say that "a state of abnormally increased muscle tonus" is by no means a prerequisite for the appearance of this reflex; it is elicited under completely normal conditions of muscle tonus. Böhme,[115] who in 1927 stated that the Trömner reflex indicates a lesion of the pyramidal tract, said in a review[120] published a year later that a weak Trömner reflex can be found in cases in which there is a functional increase of reflexes. I would put it this way: A strongly positive Trömner sign may, but need not, be a pyramidal sign.

In a recent monograph on the pyramidal signs of the upper extremity, Lange[121] stated: "The Hoffmann-Trömner reflex has in my opinion the same significance as the Babinski sign." There is not the slightest doubt that such a statement is untenable and can only lead to serious diagnostic mistakes.

In 1926 Sterling[122] recommended that the technic of Rossolimo be applied to the fingers, as well as to the toes. The examiner taps the volar surface of the patient's finger tips with a short, elastic blow with all his fingers. Flexion of all fingers follows. Sterling observed this reflex chiefly in cases of lesions of the pyramidal tract. Only in certain cases did he find it positive when there was no spastic paralysis of the corresponding extremity. In these cases the triceps and radial reflexes were exaggerated at the same time. This statement must be understood as an admission that this reflex, which is of course identical with the finger flexor reflex, is not in any way pathognomonic of a pyramidal lesion. Since a certain amount of tonus of the finger flexors is essential for the appearance of the finger Rossolimo sign, it is understandable that Johnsson,[123] on investigating the Sterling reflex in cases of early hemiplegia, found that it was absent in the first weeks, but appeared later.

Russetzki,[124] in commenting on Sterling's article, said that in 1925 he described in the Russian literature a phenomenon which exactly corresponded to Sterling's.

In 1935 Rosner[125] described a reflex which he called the "finger-thumb reflex." He, too, applied the method of Rossolimo to the fingers. Instead of tapping one or two fingers, as Trömner did, he tapped all four fingers, as Sterling did. He at first did not mention the work of Trömner or Sterling. Although he seriously attempted to emphasize the importance of his reflex as a pyramidal sign, he once mentioned that in normal persons, too, there may occur a slight bending movement of the second to the fifth finger, but he maintained that it is easy to distinguish this mild movement of the fingers from the real reflex movement. In my opinion the movements are identical; the difference is one only of degree. Although it is easy to distinguish the reflex finger flexion in a case of advanced spastic paralysis from that in normal persons, there is no way to differentiate slight

118. Voss, G.: Das Verhalten der spastischen Reflexe im Säuglings- und im frühen Kindesalter, Monatschr. f. Kinderh. **50**:331, 1931.

119. Cooper, M. J.: Mechanical Factors Governing the Trömner Reflex, Arch. Neurol. & Psychiat. **30**:166 (July) 1933.

120. Böhme, A.: Methoden der Reflexprüfung beim Menschen, in Abderhalden, E.: Handbuch der biologischen Arbeitsmethoden, Berlin, Urban & Schwarzenberg, 1938, vol. 5, pt. B, p. 619.

121. Lange, O.: Sinais piramidais nos membros superiores, Rev. Assoc. paulista de med. **18**:351, 1941.

122. Sterling, W.: Les phénomènes des doigts analogues aux signes de Babinski et de Rossolimo, Rev. neurol. **2**:82, 1926.

123. Johnsson, V.: Examination of a Hand Reflex Described by Sterling, Hygiea **97**:401, 1935; abstracted, Zentralbl. f. d. ges. Neurol. u. Psychiat. **78**:37, 1935.

124. Russetzki, J.: Sur le phénomène des doigts analogue au signe de Rossolimo décrit par W. Sterling, Rev. neurol. **1**:317, 1927.

125. Rosner, R.: Ein Zeichen der Pyramidenbahnläsion an der oberen Extremität, Wien. klin. Wchnschr. **48**:800 and 1291, 1935.

differences in the degree of flexion—differences which are of practical diagnostic importance. Rosner[125] offered another sign by which his reflex may be proved pathologic and indicative of a lesion of the pyramidal tract. If, in addition to the four fingers, the thumb makes a movement of flexion, then, he claimed, the reflex is definitely pathologic and indicates a lesion of the pyramidal tract. This statement is not correct. On elicitation of the finger flexor reflex by the method described earlier, one often sees an associated flexion of the thumb in completely normal persons. This, then, can by no means be regarded as pathologic, as Rosner assumed. Rosner later strove to point out a distinction between his method of elicitation and that of Trömner. Such a distinction is of little significance. It really does not matter whether flexion is secured by the tapping of one finger or of two (Trömner) or of all four (Rosner). In his later article Rosner[126] was more cautious in evaluating his sign as pyramidal. He stated that the presence of this reflex may, "under certain circumstances," be considered as a pyramidal sign. Zajdorf,[127] a pupil of Bing, in a comparative study of the Trömner and the Rosner reflex, found the former more sensitive, but mentioned that both may be positive in the presence of functional disease of the central nervous system. Contradictory to this is his previous statement that "the finger flexion phenomenon is a pathologic reflex that appears with a lesion of the motor tract above the seventh and eighth cervical segments."

Since any muscle can be stretched, and its reflex thus elicited at any point along its entire course, from origin to insertion, it is understandable that the finger flexor reflex can be elicited not only from the finger tips but from proximal points as well. Von Bechterew,[128] as far back as 1902, mentioned the possibility of eliciting a reflex flexion of the fingers on mechanical irritation of the volar aspect of the forearm and the hand. He mentioned in particular the reflex flexion of the fingers, hand and forearm when the tendons of the flexors above the ligamentum carpi transversum were tapped. He stressed that these reflexes are not constant, that they are often seen in normal persons and may appear extremely exaggerated under pathologic conditions. Von Bechterew's pupil Nikitin[129] obtained reflexes from the flexors of the hand bilaterally in 62 per cent of normal persons. Goldscheider[130] described the same reflex as a flexion tendon reflex which is elicited by tapping the tendons at the ligamentum carpi transversum, the hand being dorsiflexed. He obtained the same effect, even more constantly, from the flexor muscles of the forearm. Goldscheider found this reflex in 45 per cent of normal persons and observed that it was exaggerated under pathologic conditions and in patients with neuroses. Bing[117] listed under normal "tendon and bone reflexes" a flexor tendon reflex produced by a tap on the flexor tendons at the wrist joint, resulting in finger flexion. Foerster[131] designated as a finger flexor reflex a response that can be elicited from the flexor tendons on the volar side of the forearm. This reflex, he stated, is normally weak and hardly elicitable. It is greatly exaggerated under spastic conditions of the arm and can then be elicited also by tapping of the lower end of the radius and the palm of the hand. I cite these examples only to show that it is possible to elicit a finger flexor reflex from any point over the entire length of the finger flexor muscles and their tendons. Such a reflex can be elicited in normal persons.

To elicit a deep muscle reflex it is not necessary to tap the muscle or its tendon directly, but it is sufficient to produce concussion of the underlying bone by tapping it.

In 1908 Jacobsohn[132] described a finger flexion reflex which consisted of flexion of the fingers on a mild tap of the lower end of the radius or in its neighborhood on the dorsal side of the forearm. He expressed the opinion that this reflex is analogous to the Babinski sign and a valuable sign in cases of spastic paralysis affecting the upper extremities. In 1910 Babinski[133] described the same phenomenon of flexion of the fingers when the lower end of the radius is tapped as when the "radioperiosteal reflex" is elicited. He saw in it a pyramidal sign, as did Bing[117] and Russetzki.[134] The latter even

126. Rosner, R.: Der Fingerreflex—als Pyramidenzeichen der oberen Extremität, Schweiz. med. Wchnschr. 70:210, 1940.

127. Zajdorf, A.: Das Fingerbeugephänomen, Inaug. Dissert., Basel, 1937.

128. von Bechterew, V. M.: (a) On the Carpo-Phalangeal Reflex, Obozr. psikhiat., nevrol. 7:487, 1902; (b) Ueber den Carpometacarpalreflex, Neurol. Centralbl. 22:195, 1903.

129. Nikitin, M. P.: Ueber den Bechterew'schen Beugereflex der Zehen, Berl. klin. Wchnschr. 45:1643, 1908.

130. Goldscheider, A.: Diagnostik der Krankheiten des Nervensystems, ed. 4, Berlin, Gustav Fischer, 1911, p. 50.

131. Foerster, O., in von Schjerning, O.: Handbuch der ärztlichen Erfahrugen im Weltkriege, Leipzig, Johann Ambrosius, Barth, 1922, vol. 4, p. 270.

132. Jacobsohn, L.: Ueber den Fingerbeugereflex, Deutsche med. Wchnschr. 1908, vol. 2, p. 1971.

133. Babinski, M.: Inversion du réflexe du radius, Bull. et mém. Soc. méd. d. hôp. de Paris 30:185, 1910.

134. Russetzki, J.: Le syndrome pyramidal, Acta med. Scandinav. 73:286, 1930.

expressed the opinion that the reflexes of Jacobsohn and von Bechterew are "grasping reflexes," which certainly they are not. To consider as pathologic a reflex finger flexion which follows tapping of the lower part of the radius is not correct; it is at variance with experience gathered since Jacobsohn's and Babinski's publications. Curschmann[101] found that the reflex described by Jacobsohn is not infrequent in patients with neuroses, especially young hysterical and neurasthenic persons. Sahli[135] stated, in referring to the Babinski modification of the von Bechterew–Jacobsohn reflex: "I must deny the diagnostic importance of this reflex, since I have observed it in exactly the same form in normal persons." Hoge,[136] who expressed the opinion that this reflex is pathologic, observed it in a few persons—neurotic patients—who showed no other signs or symptoms of organic nervous disease. "Again and again," stated Antoni,[137] "for instance in cases of neurasthenic hyperreflexivity, I see, on tapping the end of the radius, a simultaneous jerk of the flexors of the elbow and of the fingers." Foix and Chavany[138] noted that when one tapped the processus styloides radii, one "always" observed flexion of the fingers of mild degree, together with flexion of the forearm. Wilson,[139] too, evidently concluded that this finger flexion was normal, since he spoke of the "finger flexion part of the complete radial or supinator reflex." Pitres and Testut[140] "sometimes" observed this accompanying flexion of the fingers. It is statistically impossible to determine the frequency of finger flexion on tapping of the processus styloides radii, since much depends on the direction of the blow and the position of the forearm. There can be no doubt, however, that this reflex is in essence a normal one, though sometimes not distinctly perceptible; it appears more distinctly in cases of reflex hyperirritability, of functional or organic nature. In itself it by no means indicates a lesion of the pyramidal tract.

In 1926 Kempner,[141] unaware of any former publications, described this reflex and was reminded by Jacobsohn-Lask[142] that the phenomenon had been discovered by him eighteen years previously.

Since concussion of the bones of the forearm can produce the finger flexor reflex, it is worthy of note that this flexion of the fingers can be achieved by tapping not only the radius (Babinski, Jacobsohn, and Kempner) but the posteroinferior surface of the ulna (Purves-Stewart[143]). Von Bechterew[144] noted flexion of the fingers when the acromion or the coracoid process was tapped.

In 1902 von Bechterew[128a] reported in the Russian literature a "carpophalangeal reflex" as a joint reflex. In a poor translation of this article into German,[128b] this reflex is called the "carpometacarpal reflex," under which name it has been known since. Von Bechterew's original name is more appropriate. As I mentioned in the introduction, a muscle stretch reflex may be elicited not only by tapping the side of the extremity from which the muscle originates and into which it is inserted, but by tapping the opposite, or convex, side, the joint being thus depressed and the muscle indirectly stretched. It follows therefore that the stretching of the finger flexors may be achieved by tapping the dorsum of the hand. Indeed, the reflex of von Bechterew consists of flexion of the fingers when the dorsal surface of the carpal and the adjoining part of the metacarpal bones are tapped, especially laterally.

In his first article, von Bechterew expressed the opinion that this reflex indicated a lesion of the pyramidal tract. In a later article[145] he noted that the reflex appears in cases of increased reflex irritability. Galant[146] called it pathologic, and Jacobsohn[132] and Lewandowsky[147] found it associated only with organic lesions of the pyramidal tract. Galant[146] was able to elicit the reflex also by tapping the metacarpophalangeal and the interphalangeal joint lines. Since the reflex is nothing but a finger flexor reflex, it cannot be regarded as pathologic. In line with

135. Sahli, H.: Lehrbuch der klinischen Untersuchungsmethoden, ed. 7, Leipzig, Franz Deuticke, 1932, vol. 3, p. 224.

136. Hoge, M. W.: The Radio-Phalangeal Reflex in Lesions of the Pyramidal Tract, Interstate J. Med. 19:787, 1912.

137. Antoni, N.: Zur Kritik der irrtümlich sogenannten Sehnen- und Periostreflexe, Acta psychiat. et neurol. 7:9, 1932.

138. Foix and Chavany, in Roger, G. H.; Widal, F., and Teissier, P. J.: Nouveau traité de médecine, Paris, Masson & Cie, 1928, vol. 18, p. 574.

139. Wilson, S. A. K.: Neurology, London, Edward Arnold & Co., 1940, vol. 2, p. 1309.

140. Pitres, A., and Testut, L.: Les nerfs en schémes, Paris, Gaston Doin, 1925, p. 687.

141. Kempner: Ueber eine Art Mendelschen Reflexes an der Hand, Klin. Wchnschr. 5:1255, 1926.

142. Jacobsohn-Lask, L., in discussion on Kempner,[141] p. 1471.

143. Purves-Stewart,[108] p. 536.

144. von Bechterew, V. M.: On the Acromion or Apical Reflex, Obozr. psikhiat., nevrol. 7:181, 1902.

145. von Bechterew, V. M.: Ueber Reflexe distaler Abschnitte der oberen Extremität und über ihre diagnostische Bedeutung, Neurol. Centralbl. 24:392, 1905.

146. Galant, S.: Die Reflexe der Hand, Ztschr. f. d. ges. Neurol. u. Psychiat. 43:260, 1918.

147. Lewandowsky,[80] p. 605.

this concept are the observations of Goldstein,[148] who noted von Bechterew's carpometacarpal reflex in cases of purely functional nervous disorders, such as neuroses with increased general reflex irritability. Investigations in Sahli's[185] clinic proved that this reflex occurs also in normal persons. Bickel[149] emphasized that it may be elicited in cases in which there is only mild functional reflex hyperirritability. Beck[150] found that von Bechterew's carpometacarpal reflex was more or less distinct in normal persons when the hand was dorsiflexed at the wrist joint, i. e., when the flexors of the fingers were stretched. It is interesting that Beck found this reflex reversed, dorsiflexion of the fingers taking place when the dorsum of the hand was tapped if the hand was volar flexed.

Since von Bechterew's investigations, different methods have been described for elicitation of finger flexion by tapping parts of the dorsum of the hand: Sicard and Cantaloube[151] elicited a "reflex of the thumb, index, little finger and interosseous muscles"; Niculesco,[152] a "reflex of the interosseous muscles," a "metacarpothenar reflex" and a "metacarpohypothenar reflex," and Coppa,[153] a "reflex of the fifth metacarpal bone." The work of all these men proved only that one can effect stretching of a single finger flexor, and thus elicit reflex flexion of a single finger, from any point over the dorsum of the hand or of the metacarpal bones. It is of course easier to effect stretching of a finger flexor by direct tapping of the volar surface of the finger tips than by the indirect method, namely, tapping of the dorsum of the hand or the radius. Thus it is understandable that Sterling[122] found the finger Rossolimo sign twice as common as the reflex of Jacobsohn and that Johnsson[154] found it the most common of all signs and phenomena which supposedly indicate a pyramidal lesion. But all the aforementioned

reflexes which are characterized by flexion of the fingers represent one and the same reflex, which reflex may be more easily elicited by one method than by another. The ease with which the finger Rossolimo sign can be elicited distinctly in the presence of the slightest pyramidal lesion is due simply to the fact that this reflex is basically normal and the most minute increase in tonus is sufficient to make it distinct.

The identity of the finger flexor reflex and other so-called tendon (i. e., muscle stretch) reflexes is shown also by the fact that with pyramidal lesions the finger flexors show a clonus of the same character as the quadriceps muscle (patellar clonus) and the muscles of the foot (ankle clonus). Noïca[155] pointed out the similarity of these three clonuses.

All the adjectives and proper names which have been used to designate this reflex of the finger flexors, and all those that may follow—since there is probability of further "rediscovery" and development of new technics of elicitation—belong in a book on the history of neurology. In any textbook of neurology belongs *one* name—the finger flexor reflex. In describing a case, Johnsson[154] stated: "The hand Rossolimo sign (Sterling's reflex) and the Trömner reflex were positive on the right side." Would it not be simpler, instead of using these three names, to say plainly: "The finger flexor reflex was positive"?

HAND FLEXOR REFLEX

Exactly as do the flexors of the fingers, so do the flexors of the hand react to brisk stretching with contraction. This constitutes the hand flexor reflex. The technic is identical. The two reflexes are often elicited at the same time. The tendons of the flexors of the hand may be tapped on the volar side of the forearm at the ligamentum carpi transversum or higher. The same reflex may be elicited by a tap on the dorsum of the hand or of the forearm while the hand is loosely supported at the palm by the examiner. Here the direction of the blow is important. This reflex is not constant, but certainly appears in normal persons and is greatly exaggerated in patients with pyramidal lesions, occasionally even to the state of hand clonus. This clonus appears only when other, and more striking, signs had appeared earlier; it is hardly necessary to give it a special name: The term the "hand phenomenon of Dejerine"[156] has sometimes been used. Of course the extensors of the hand react,

148. Goldstein, M.: Die Gelenkreflexe der Hand und ihre klinische Bedeutung, Ztschr. f. d. ges. Neurol. u. Psychiat. **61**:1, 1920.

149. Bickel, H.: Ueber die diagnostische Bedeutung der Knochenreflexe, Deutsche med. Wchnschr. **38**:2399, 1912.

150. Beck, E.: Reflexbiologische Studien, J. f. Psychol. u. Neurol. **29**:216, 1923.

151. Sicard, J. A., and Cantaloube, P.: Les réflexes musculaires du pied et de la main, Presse méd. **24**:145, 1916.

152. Niculesco, I.: Le réflexe des interosseux, abstracted, Rev. neurol. **28**:384, 1921.

153. Coppa, E.: Contributo allo studio della reflettività della mano in condizioni patologiche, Cervello **7**:164, 1928.

154. Johnsson, V.: Case of Operated Tumor of Spinal Cord with Inversion of Radial Reflex and Facial Paralysis, Hygiea **96**:625, 1934; abstracted, Zentralbl. f. d. ges. Neurol. u. Psychiat. **75**:685, 1935.

155. Noïca: Phénomènes réflexes par distension tendineuse, Rev. neurol. **26**:196, 1919.

156. Dejerine, J.: Sémiologie des affections du système nerveux, Paris, Masson & Cie, 1926, p. 946.

too, on brisk stretching with contraction. Such a reflex has been described by von Bechterew [145] as the "hand reflex" (percussion of the dorsal part of the lower part of the ulna) and by Sandoz [157] as a pathologic reflex of the upper extremity (percussion of the lower part of the radius). Dagnini,[158] who described this phenomenon as a "reflex of hand extension," was in error when he stated that it had never been described before. In order to elicit these reflexes a certain position of the hand and the forearm is necessary. The percussion brings about the dorsal extension of the hand. These reflexes of the extensors of the hand are clinically insignificant.

FINGER-THUMB REFLEX (MAYER)

This reflex was described by Mayer [159] in 1916. He first called it the "finger-thumb reflex" and then the "metacarpophalangeal reflex." The first name is more appropriate. In exceptional cases it is necessary, in order to avoid confusion with other reflexes, to add the proper name. This reflex consists of opposition and adduction of the thumb combined with flexion at its metacarpophalangeal joint and extension at its interphalangeal joint on firm passive flexion of the third to the fifth finger—especially the fourth finger—at the proximal joints. This reflex is positive in normal persons and absent in patients with pyramidal lesions. Though it may be absent bilaterally in normal persons, its unilateral absence constitutes one of the most delicate of the pyramidal signs. Because it is not a muscle stretch reflex, this reflex properly does not belong here but should be included with the postural reflexes. It is essentially a part of the "negative support reaction." It is mentioned briefly here to emphasize a practical point, disregard of which may lead to erroneous diagnostic conclusions. Not only may this reflex be lost but it may be exaggerated, and this may occur with a lesion of the frontomotor region of the brain. This exaggeration may be the only striking localizing sign. In such a case it may be extremely difficult to say on which side the reflex must be regarded as normal and on which as exaggerated or diminished. It must be assumed that this reflex, the arc of which passes through the cortex of the motor area, is inhibited by the premotor area.

PRONATOR REFLEX

When the volar surface of the lower part of the radius is tapped so that a jerky supination is effected, and the pronators are stretched, these pronators (the pronator teres and pronator quadratus muscles) contract briskly. This constitutes the pronator reflex. This reflex has been described under a diversity of names, such as "ulnar reflex," "radial-pronator reflex," "ulnar-pronator reflex" and "cubitopronator reflex." Landau [160] distinguished (*a*) a radial pronation reflex, (*b*) an ulnar pronation reflex and (*c*) a superior radial pronation reflex. These variously named reflexes differ only in that they are elicited by tapping different points. In all of them, however, it is the contraction of the same pronator muscles which constitutes the reflex. Therefore this reflex, regardless of the point of its elicitation, should be called pronator reflex, as von Bechterew [145] did in 1905. This phenomenon is best elicited when the forearm is resting on its ulnar border, either vertically or pronated at a slight angle. The aim of the tap is to bring about a slight, brisk supination. Suppose the left arm is before the examiner in a position for elicitation of the pronator reflex. The forearm may be compared to a vertical column which must be tipped to the right. This can be achieved either by pushing the top of the column to the right or by pushing its base to the left. In either case the effect will be the same— the column will tip to the right. So with the forearm; when one taps the volar surface of the lower end of the radius or the dorsal surface of the styloid process of the ulna or the fourth and fifth metacarpal bones, the same effect, namely, supination and stretching of the pronators, follows. It is hardly necessary, therefore, to report that there was loss of the cubitopronator and radiopronator reflexes, as Guillain [10] did, or to distinguish a radio pronator reflex and an ulnopronator reflex, as Monrad-Krohn did.[161] There is but one reflex. There are other ways by which one may elicit the response, for instance, by tapping the elbow laterally from the medial epicondyle at the point of origin of the pronator teres muscle. Tapping the lower end of the radius or the ulna, however, is by far the better method. A subtle technic is essential here. The reflex hammer must swing loosely; the tap must be soft and so directed as to effect stretching of the pronators exclusively or predominantly. The position of the forearm is important.

157. Sandoz, P.: Sur un réflexe pathologique des membres supérieurs, Rev. méd. de la Suisse Rom. **32**: 533, 1912.

158. Dagnini, G.: Réflexe d'extension de la main dans les lésions des voies pyramidales, Rev. neurol. **1**: 413, 1934.

159. Mayer, C.: Zur Kenntnis der Gelenkreflexe der oberen Gliedmassen, Neurol. Centralbl. **35**:11, 1916.

160. Landau, E.: Neuropathologische Kriegserfahrungen, Cor.-Bl. f. schweiz. Aerzte **44**:33, 1919.

161. Monrad-Krohn, G. H.: The Clinical Examination of the Nervous System, ed. 7, New York, Paul B. Hoeber, Inc., 1938, p. 127.

If this position is changed, the direction of the blow altered or the force of the blow increased, stretching of other muscles will result—for instance, the biceps, the brachialis, the triceps, the flexors of the hand and fingers or the extensors of the hand. One elicits completely different reflexes and their combinations, in strict dependence on the position of the forearm and the direction of the stroke. This variation was pointed out by von Bechterew[115]; Bickel[149]; Marie, Bouttier and Bailey[162]; Poppi,[163] and Antoni.[137] On careful clinical observation it is easy for any one to see the mechanism by which remote muscles are influenced by a single tap, especially in examination of a patient with muscular hypertonia. Here the absolute and direct dependence of a reflex movement on the stretching of the respective muscles is self evident. The reflexes appear unmistakably as direct results of stretching of the muscles. One does not need to assume, as Foerster[161] did, that some of the reflexes described here may also be due to stimulation of the receptors of the bones. Foerster spoke of these reflexes as "bone phenomena,"

while Goldstein[148] called them "periosteal reflexes"; yet they are nothing else than muscle stretch reflexes.

The clinical importance of the pronator reflex is considerable, especially in the diagnosis of an early lesion of the pyramidal tract affecting the arm. With such a lesion an increase in the tonus of the pronator muscles and the tendency of the forearm to assume a position of pronation may constitute one of the initial signs (Gierlich[165]). In later stages this tendency to pronation may be pronounced; the hypertonia of the pronators may be so increased that on brisk, passive supination a clonus may be elicited. The increase of the pronator reflex goes hand in hand with tension in the pronator muscles. Thus a slight unilateral exaggeration of the pronator reflex may be one of the first signs of a pyramidal lesion affecting the arm. In doubtful cases it is advisable to combine the examination of the pronator reflex with a test for hypertonia of the pronator muscles: Holding, loosely, the forearm of the patient, the examiner, with brisk, jerky, passive movements, brings the arm into a position of supination.

University of California Hospital.

162. Marie, P.; Bouttier, H., and Bailey, P.: Les supino-réflexes du membre supérieur, Rev. neurol. **29:** 451, 1922.

163. Poppi, U.: Bemerkungen über den Ulno-Pronator-Reflex, Wien. med. Wchnschr. **77:**59, 1927.

164. Foerster,[65] vol. 5, p. 175.

165. Gierlich, N.: Ueber das Promationsphänomen der Hand als frühes Kennzeichen einer Läsion der Pyramidenbahn, Deutsche Ztschr. f. Nervenh. **84:**69, 1925.

A SIMPLE METHOD OF DETERMINING FREQUENCY SPECTRUMS IN THE ELECTROENCEPHALOGRAM

OBSERVATIONS ON EFFECTS OF PHYSIOLOGIC VARIATIONS IN DEXTROSE, OXYGEN, POSTURE AND ACID-BASE BALANCE ON THE NORMAL ELECTROENCEPHALOGRAM

GEORGE L. ENGEL, M.D.; JOHN ROMANO, M.D.; EUGENE B. FERRIS Jr., M.D.; JOSEPH P. WEBB, M.D., AND CHARLES D. STEVENS, Ph.D.

CINCINNATI

Although the gross configuration of the normal electroencephalogram remains remarkably constant in the same person from day to day, and even from year to year, there is nevertheless a significant physiologic zone of variation in frequency, voltage and regularity, which often cannot be appreciated by inspection alone. The fundamental elements controlling brain potentials have been defined by Dubner and Gerard [1]; they include the intrinsic metabolic activity of the individual cells, the cellular membrane charges and the composition of the surrounding fluid mediums. As recorded by the electroencephalograph, the brain waves represent the electrical activity of masses of cortical cells discharging in a synchronous fashion. The nature of this synchronizing factor has not yet been clarified, but it may involve a group of cells acting as pacemakers. Alterations in the determinants of cellular metabolism, in membrane charge or in the composition of the surrounding fluid mediums generally affect frequency and voltage first, while regularity, which is an index rather of the synchronizing activity of the theoretic pacemaker mechanism, is influenced by more pronounced changes in these factors. In addition, the pacemaker mechanism is influenced by higher neural factors concerned with levels of attention and consciousness, such as those involved in opening the eyes or in falling asleep. These factors usually lead to abrupt changes in frequency, and they were controlled in this study.

The effects of gross alterations in the sugar, carbon dioxide and oxygen contents of the blood have been known for many years. Less well recognized are the effects of changes in some of these factors within a more physiologic range. An analysis of the magnitude of such physiologic effects is of value in two respects: First, observations on the effects of noxious factors, such as alcohol, drugs, anoxia and changes in atmospheric pressure, may be subject to errors in interpretation if the range and role of the major physiologic variables have not been previously assayed. Second, delineation of the zone of response to physiologic variables in normal subjects furnishes a valuable guide to study of similar responses in persons with disease states. In this respect the concept of threshold may prove useful.

The first quantitative analysis of the cortical frequency spectrum during both physiologic and pathologic alterations in constituents of the blood was made by Gibbs, Williams and Gibbs,[2] using the Grass-Fourier transform method.[3] This method of analysis yields a continuous spectrum of the energy in all frequencies from 1 to 60 per second in a strip of record of thirty seconds' duration. This study revealed shifts in distribution of energy during both physiologic and pathologic ranges of the various constituents of the blood. In other studies of this nature it has been attempted only to quantitate the total amount of normal activity (i. e., the per cent time alpha) or the total amount of abnormal activity (i. e., the delta index), and hence such investigations have been of limited value in the demonstration of continuous change through physiologic and pathologic zones.

For the purposes of clinical investigation there is real need for a simple method of determining frequency spectrums. Unfortunately, the Grass method is not available to most investigators. Further, it gives a rather complex expression of the distribution of frequencies, the analysis

1. Dubner, H., and Gerard, R. W.: Factors Controlling Brain Potentials in the Cat, J. Neurophysiol. 2:142, 1939.

2. Gibbs, F. A.; Williams, D., and Gibbs, E. L.: Modification of the Cortical Frequency Spectrum by Changes in Carbon Dioxide, Blood Sugar, and Oxygen, J. Neurophysiol. 3:49, 1940.

3. Grass, A. M., and Gibbs, F. A.: A Fourier Transform of the Electroencephalogram, J. Neurophysiol. 1:521, 1938.

of which is no small problem in itself. Gibbs and his associates [2] stated:

. . . One cannot say what part of the energy at a given frequency is derived from relatively pure sine waves, which would appear as discrete and countable waves of that frequency in the unanalyzed record, and what part is derived from non-sinusoidal slower frequencies, the faster components of which are quite properly recorded as higher frequencies.

The complete objectivity of the method has much in its favor; one wonders, on the other hand, to what extent the indiscriminate analysis of all base line swings and superimposed oscillations includes artefacts of noncortical origin. Arrangement of the apparatus so that a simultaneous ink record is obtained does much to eliminate this objection.

Another method used by many investigators from time to time since the electroencephalogram has been known is simply the measurement of the wavelengths of successive waves. This method is exceedingly tedious and difficult, and for this reason alone it has never achieved any great popularity.[4]

It is our purpose in this paper to report on a simple quantitative method of expression of frequency distribution which has proved useful in the analysis of both normal and abnormal electroencephalograms. With this method of study of the normal electroencephalogram data on the effects of (physiologic) variations in the sugar and oxygen contents of the blood and of changes in posture are presented. Observations on hyperventilation, not properly a normal physiologic experience, during variations in the level of the blood sugar and in posture are also included because hyperventilation is commonly used by electroencephalographers as a diagnostic procedure. The conditions determining the appearance of slow waves during hyperventilation are of obvious importance.

METHODS AND MATERIAL

Electroencephalographic Method. — The instrument used was the standard, push-pull, ink-writing apparatus, constructed by Mr. Albert Grass. Bipolar fronto-occipital tracings were taken in all instances. In these studies regional variations were not considered. The

---

4. Since this paper has been written, a new method of analysis of electroencephalograms, devised by W. Gray Walter (Appendix on a New Method of Electro-Encephalographic Analysis, J. Ment. Sc. **89**:222, 1943), has come to our attention. The equipment consists of a series of tuned reeds, covering the stretch from 1 to 20 cycles per second, which are energized by the output from the electroencephalograph. The apparatus is ingeniously arranged so that each ten second strip of record has traced over it a histogram of its spectrum. Gray stated that the analyzer shows a clear distribution of energy responding to physiologic stimuli, but no data are presented in this preliminary report.

usual precautions against extraneous interference, electrical and other kinds, were employed.

Analysis of Frequency Spectrums.[5]—With the usual ruled paper (large divisions at one second intervals), the number of complete waves in each one second strip of record was counted. The count for a total of 300 one second intervals was made, and the distribution of frequencies per second was expressed as a percentage of the whole. A complete wave was one which returned at least two thirds of the way to the base line. A wave which crossed the line dividing adjacent one second intervals was counted in the interval containing more than half the wave. Small superimposed waves were not counted. In general, it was found advisable to make full use of the high frequency filter to damp the superimposed fast oscillations of very low voltage (some of which were of muscle origin) so that the basic sine waves would have sharper definition. Stretches of low voltage fast activity, which were present in varying degrees in all records, were designated as such, and no attempt was made to estimate the individual waves, which were often not countable. When a given interval contained both countable waves and low voltage fast activity, the type which occupied the greater portion of that interval was arbitrarily selected for purposes of designation.

Such an analysis yields a "spectrum" of frequencies ranging from 1 to 12 per second, together with some low voltage activity. It should be emphasized, however, that this is not a true spectrum of frequencies in that the percentages of one second intervals containing 8 waves, 9 waves, 10 waves, etc., rather than the percentages of 8 per second waves, 9 per second waves, 10 per second waves, etc., are given. In other words, the distribution of waves per second, rather than the distribution of individual wavelengths, is determined. The latter is a tedious process and involves measurement of the length of each wave with a caliper of some sort. Our method may give a slightly false impression of the distribution of wavelengths greater and less than the dominant one, for waves of these frequencies will tend to be averaged with waves of the dominant frequency and hence may appear in somewhat lower proportion than is actually the case. For example, if 2 or 3 waves of 5 per second frequency should appear with 8 per second waves in a one second interval, the number of waves in that interval would be recorded as 6 or 7, and the figure would not reveal the presence of 5 per second waves. This will not obscure any shift toward faster or slower frequencies, and no error in interpretation will result if it is remembered that the method gives the distribution of average frequencies per second rather than the distribution of wavelengths. For practical purposes the method has proved thoroughly satisfactory in establishment of the magnitude of shifts in frequency under conditions in which such changes have been diffuse rather than paroxysmal. When the changes are paroxysmal (i. e., in epileptic records), a much longer strip must be analyzed before an accurate spectrum can be obtained.

Figure 1 illustrates the actual count of a sample record. Obviously, the more regular the record, the easier and more accurate is the analysis. Also, records with less than 50 per cent of low voltage fast activity are more satisfactory for determination of shifts within the range of countable frequencies, unless much longer strips are used. With increasing abnormality there is usually a corresponding increase in irregularity, but the resulting increased difficulty in counting is not a

---

5. One of us (G. L. E.) is primarily responsible for developing this method.

serious drawback, for the irregular waves are usually abnormally slow and hence yield a spectrum easily distinguished from normal. The practicability of the method for the study of changes in diffusely abnormal records has been demonstrated in another report on the reversible electroencephalographic changes associated with delirium.[6] In comparison of successive records it is sometimes helpful to plot the spectrums. Figure 2 illustrates typical spectrums.

With very regular records it was found sufficient to count a two hundred record strip. In these studies three hundred second strips were counted, except on the records taken during hyperventilation, which were three minutes (one hundred and eighty seconds) in length. An experienced person can count a three hundred second strip in ten minutes.

Methods of Chemical Analysis.—The dextrose content of the blood was determined by the Folin-Wu colorimetric method. The carbon dioxide and oxygen contents of arterial blood were measured by the Van Slyke manometric technic. The p_H of arterial blood was determined by means of the Leeds and Northrup

Gibbs and associates,[2] using the Grass analyzer, demonstrated an increase in energy in the slow frequencies as the blood sugar fell from 105 to 74 mg. per hundred cubic centimeters, while with a rise in the sugar content of the blood from 202 to 480 mg. per hundred cubic centimeters there was a slight shift to the fast side of the spectrum. Davis,[7] in a study of 40 healthy college students, found that as the blood sugar fell to a minimum of 53 to 83 mg. per hundred cubic centimeters the normal alpha activity of the electroencephalogram was increasingly replaced by slower waves, chiefly in the 6 to 8 per second range. No correlation between the magnitude of the shift and the levels of the blood sugar was attempted.

Method.—Eleven subjects were studied. Ten received an intravenous infusion of 0.5 Gm. of dextrose per

Fig. 1.—A sample electroencephalogram, illustrating the technic of counting waves.

potentiometer and glass electrode, the phosphate buffer of the Bureau of Standards being used as reference. Partial pressures of carbon dioxide and base bicarbonate concentrations were determined from Shock and Hasting's nomogram.

Material.—Twelve healthy men, medical students and physicians, ranging in age from 23 to 56 years, volunteered as subjects for these studies.

CHANGES IN DEXTROSE CONTENT OF THE BLOOD

The effects on the normal electroencephalogram of hypoglycemia of clinical magnitude are well known and need no further discussion.

kilogram of body weight as a 10 per cent solution of dextrose in distilled water, administered over a period of thirty minutes. Sugar levels were determined for blood from a vein in the arm, and electroencephalographic tracings were taken in the fasting, preinfusion state, at the end of the infusion and one, two and two and one-half hours after infusion. All examinations were made with the patient in the recumbent position. One subject was studied after a high carbohydrate breakfast and again eleven hours later, when the level of the blood sugar was much lower.

Results.—Electroencephalograms may be divided into two types: records with more and records with less than 70 per cent alpha (8 to 12 per second) activity. As has been pointed out by other observers, the presence of high or of low alpha activity is a constant characteristic

6. Romano, J., and Engel, G. L.: Studies of Delirium: I. Electroencephalographic Data, to be published. Engel, G. L., and Romano, J.: Studies of Delirium: II. Reversibility of the Electroencephalogram with Experimental Procedure, Arch. Neurol. & Psychiat., to be published.

7. Davis, P. A.: Effect on the Electroencephalogram of Changing Blood Sugar Level, Arch. Neurol. & Psychiat. 49:186 (Feb.) 1943.

of the individual record. Five records showed high alpha activity; 5 records, low alpha activity, and 1 record. well developed alpha activity from the right cortex and poor alpha activity, with many low voltage fast waves and some irregular slow rhythm from the left cortex. This subject had had speech difficulties (stammering and stut-

no subject experienced any symptoms suggestive of hypoglycemia. When 6 to 7 per second activity was present in the fasting state, it disappeared when the blood sugar became higher and, conversely, it increased in amount as the blood sugar fell below the fasting levels. The first column (*A*) in figure 2 illustrates the frequency spec-
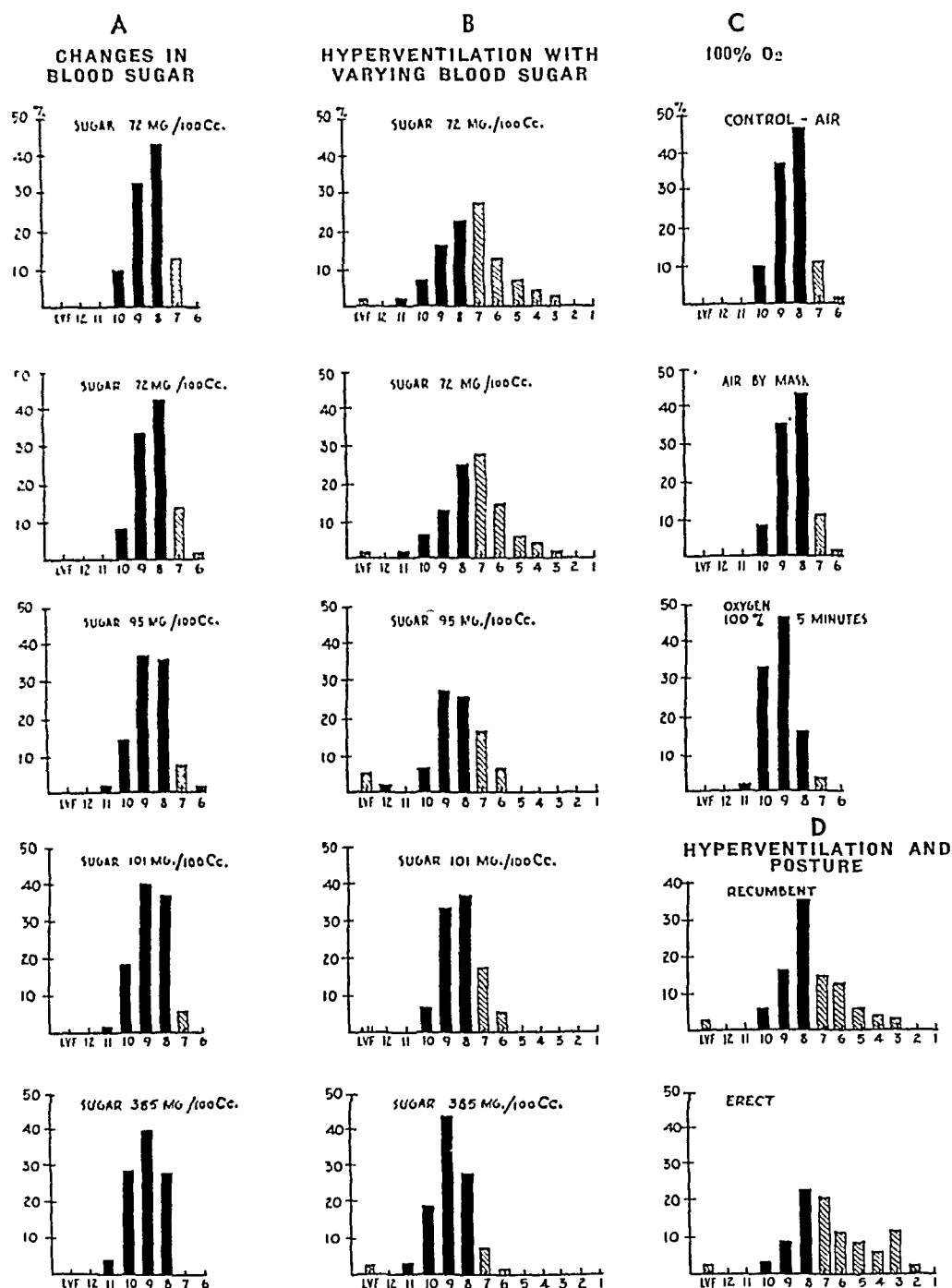
Fig. 2.—Spectrums showing the effects of variations in blood sugar (*A*), of hyperventilation and variations in blood sugar (*B*), of inhalation of oxygen and compressed air (*C*) and of hyperventilation and posture (*D*) in a single subject.

tering) as a child, but at the time of study he revealed no neurologic abnormalities.

Examination of table 1 reveals that in the records with dominant alpha rhythm (nos. 1 to 6) there was a shift toward faster frequencies with higher levels of the blood sugar and toward slower frequencies with lower levels of the blood sugar. There were no levels of the blood sugar under 70 mg. per hundred cubic centimeters, and

trums of one subject during an intravenous dextrose tolerance test.

In the records with poor alpha rhythm no consistent trends in the frequency spectrums were observed. It is believed that this was due, at least in part, to the difficulty in counting these more irregular records and to the fact that an insufficient sample of countable frequencies was available in the three hundred second stretch.

TABLE 1.—*Effect of Level of Dextrose in the Blood on Frequency Spectrums in the Electroencephalogram* [*]

Subject	Status [†]	Blood Sugar, Mg. per 100 Cc.	Electroencephalographic Frequency Spectrums, Percentages									Alpha Activity (8-12/Sec.)
			LFV [‡]	12/Sec	11/Sec.	10/Sec.	9/Sec.	8/Sec.	7/Sec.	6/Sec.	5/Sec	
E. B. Г. Age: 37	2½ hr...	72	..	..	..	10	33	43	13	..	..	86
	2 hr.......	..	..	..	..	8	34	43	14	1	..	85
	Fasting...	95	..	..	1	15	37	36	8	1	..	90
	1 hr......	101	..	..	1	18	40	36	5	..	..	95
	End of infusion....	385	..	..	3	29	40	28	..	..	..	100
G E Age: 28	2 hr........	72	..	..	..	21	55	23	1	..	..	99
	2½ hr....	76	..	.	..	26	55	18	1	..	..	99
	Гasting..	86	.	..	..	26	63	10	..	..	..	100
	1 hr.......	120	..	..	1	34	48	16	1	..	..	99
	End of infusion . .	290	..	..	1	33	61	5	..	..	..	100
J R Age. 34	2½ hr.. .	76	..	..	..	11	41	35	11	2	..	87
	2 hr....	79	2	..	..	13	40	36	9	..	..	89
	Fasting.	100	..	..	1	10	64	22	3	..	..	97
	1 hr....	122	..	..	..	16	58	23	1	..	..	97
	End of infusion .	342	..	..	2	24	59	15	..	..	..	100
L S Age: 32	3 hr.... .	81	19	2	15	37	23	3	..	..	..	81
	2½ hr..	85	16	.	14	46	17	7	..	..	..	84
	2 hr....	109	12	..	26	43	17	2	..	..	..	88
	Fasting..	127	15	2	14	47	19	2	..	..	..	85
	1 hr......	195	8	2	22	46	15	7	..	..	..	92
	End of infusion	303	13	14	40	28	4	1	..	..	..	87
G. G. Age. 45	8 hr. fast. ...	99	5	..	6	35	36	15	3	..	..	95
	After dextrose, orally	180	1	1	11	49	31	7	..	..	..	99
J McM Age 26 right cortex	2½ hr... .	83	21	..	1	13	30	23	10	2	..	67
	2 hr ...	90	23	..	..	12	27	28	9	1	..	67
	1 hr. .	103	18	..	2	38	27	13	2	..	..	80
	Fasting ...	107	24	..	2	20	25	26	3	1	..	73
	End of infusion	240	14	..	3	46	26	10	1	..	..	85
Left cortex	2½ hr.	83	55	..	..	5	6	14	13	7	..	25
	2 hr...	90	44	..	..	1	10	20	16	9	..	31
	1 hr.....	103	60	..	..	2	12	12	10	4	..	26
	Fasting	107	52	..	..	2	6	16	16	7	..	24
	End of infusion.. .	240	63	..	..	2	9	13	12	1	..	24
M B Age: 57	2½ hr....	84	64	5	16	10	5	..	..	..	..	36
	Fasting .	91	53	..	7	18	17	5	..	..	..	47
	2 hr	93	32	3	23	33	8	1	..	..	..	68
	1 hr..... .	107	42	2	10	32	13	1	..	..	..	58
	End of infusion	215	67	1	16	11	5	..	..	..	..	33
J. W. Age: 29	2 hr...... . .	70	47	2	6	13	22	10	..	..	..	53
	2½ hr.......	83	50	..	1	16	21	11	1	..	..	49
	Fasting	95	45	2	8	20	21	4	..	..	..	55
	1 hr...... . .	103	47	..	4	16	21	12	..	..	..	53
	End of infusion. ...	265	43	..	4	20	16	16	..	..	..	57
H R. Age: 29	1 hr..	70	39	..	1	12	21	23	3	1	..	57
	2 hr.... .. .	76	39	..	..	7	19	25	8	2	..	51
	2½ hr......	82	47	..	1	19	10	24	5	..	..	49
	Fasting....	98	26	..	8	21	25	12	5	2	..	66
	End of infusion ...	163	41	1	2	15	18	18	6	..	.	54
R. K Age. 42	1 hr.........	71	76	..	2	2	8	8	..	..	..	20
	2 hr..... .. .	87	84	..	..	3	9	4	..	..	..	16
	2½ hr....	88	86	..	1	2	3	8	.	..	..	14
	Fasting..... .	92	88	..	1	3	3	5	..	..	..	12
	After infusion . .	157	82	..	1	5	8	4	..	..	..	18
R McM. Age: 25	2½ hr.....	76	92	2	2	2	2	..	..	..	..	8
	2 hr...... .	82	88	1	2	2	2	4	1	..	..	7
	Fasting....	95	90	1	4	3	1	1	..	..		10
	1 hr........ . .	131	90	5	2	3	..	..	..	..	..	10
	End of infusion... .	280	79	3	11	5	2	..	..	..	..	21

* Values are listed in order of increasing blood sugar levels.
† In this column, the number of hours indicates the period after the end of infusion
‡ In this table, and in the following tables, LVF means low voltage fast activity.

138

It is also obvious from the data that the amount of alpha activity (and, conversely, the amount of low voltage fast activity) was independent of the level of the blood sugar.

Comment.—The magnitude of the changes observed is relatively small and is not likely to introduce any error in routine examination. of dextrose as the major substrate for cerebral metabolism. The electrical frequency spectrum of the cortex apparently responds to changes in levels of the blood sugar within the normal and the hyperglycemic range, as well as in the hypoglycemic range, and in this respect the observa-

TABLE 2.—*Effect of Inhalation of 100 Per Cent Oxygen on Frequency Spectrums in the Electroencephalogram*

Subject	Experimental Procedure	LVF	12/Sec.	11/Sec.	10/Sec.	9/Sec.	8/Sec.	7/Sec.	6/Sec.	Alpha Activity (8-12/Sec.)	Blood Sugar, Mg. per 100 Cc.	Comment
G. E. Age: 29	Before	..	..	..	25	51	24	..	..	100	...	
	Air by mask	..	..	..	27	47	24	..	..	100	...	
	100% oxygen	..	..	..	30	56	13	..	..	...	...	
	Before	1	..	..	21	44	29	5	..	94	110	
	100% oxygen, 5 min	..	..	..	35	53	12	..	..	100	110	
	100% oxygen, 7 hr	..	..	..	36	51	13	..	..	100	100	Continuous inhalation of oxygen, 7 hr.
	Before	2	..	2	31	48	16	2	..	94	85	
	100% oxygen, 5 min	1	..	..	38	50	11	..	..	99	85	
E. B. F. Age: 37	Before	..	..	..	10	38	48	11	1	88	...	
	Air by mask	..	..	..	9	36	43	11	1	88	...	
	100% oxygen, 5 min	..	..	1	32	47	17	3	..	97	...	
	After 5 min	..	..	..	10	44	37	9	..	91	...	
	Before	..	..	..	8	35	42	13	3	85	123	
	100% oxygen, 5 min	2	..	..	7	43	38	9	1	88	123	
	Before	1	..	..	6	37	39	16	1	82	115	
	100% oxygen, 5 min	..	..	1	21	49	24	6	..	94	115	
	100% oxygen, 7 hr	..	..	..	16	48	29	7	.	94	96	Continuous inhalation of oxygen, 7 hr.
	Before	..	..	..	10	47	37	6	..	94	109	
	100% oxygen, 8 min	..	..	1	31	45	21	2	..	98	109	
G. G. Age: 45	Before	1	1	11	49	31	7	..	..	99	180	
	100% oxygen, 10 min	1	..	13	47	24	5	..	..	99	180	
	100% oxygen, 8 hr	..	2	14	45	30	9	..	..	100	113	Continuous inhalation of oxygen, 8 hr.
J. R. Age: 35	Before	..	..	..	13	52	34	1	..	99	...	
	Air by mask	..	..	..	12	53	31	4	..	96	...	
	100% oxygen, 5 min	..	..	..	19	59	20	2	..	98	...	
	Before	..	..	..	20	52	25	3	..	97	96	
	100% oxygen, 5 min	..	..	..	35	48	17	..	..	100	96	
	Before	..	..	..	14	61	23	2	..	98	87	
	100% oxygen, 5 min	..	..	..	32	55	12	1	..	99	99	Inhalation of oxygen started 40 min. after control
	100% oxygen, 8 hr	..	..	..	29	53	17	1	..	99	99	Continuous inhalation of oxygen, 8 hr.
H. R. Age: 20	Before	54	..	5	12	15	6	1	..	35	84	
	100% oxygen, 5 min	44	1	11	18	11	5	..	..	46	84	
	100% oxygen, 8 hr	28	1	16	21	18	13	3	..	69	97	Continuous inhalation of oxygen, 8 hr.
M. B. Age: 56	Before	32	6	20	25	15	2	..	..	68	72	
	100% oxygen, 5 min	24	10	27	22	15	2	..	..	76	72	
F. B. Age: 30	Before	72	3	4	14	6	1	..	..	28	109	
	100% oxygen, 5 min	79	5	11	3	2	..	..	..	21	109	
	100% oxygen, 8 hr	78	5	10	5	2	..	..	..	22	111	Continuous inhalation of oxygen, 8 hr.

However, in any studies of frequency spectrums during exposure to such factors as drugs, toxic substances and altered environmental conditions, particularly at threshold zones, it is apparent that changes in blood sugar during the course of the experiment must be controlled.

The mechanism of the effect of dextrose is not obvious but is possibly related to the role tions of Gibbs and his co-workers[2] are confirmed.

EFFECT OF INHALATION OF 100 PER CENT OXYGEN

The effects of low oxygen tensions have been described by other investigators and need not be discussed here. It is of some theoretic interest to know whether supernormal oxygen tensions

have any effect on the cortical frequency spectrums. Studies in which inhalation of 100 per cent oxygen is necessary during control periods (for example, high altitude exposure) make this of some practical interest. Gibbs and associates,[4] using rabbits, found no change in cortical frequency spectrums until the oxygen pressure was raised to 35 pounds (15.9 Kg.) of pure oxygen, and then there tended to be an increase in faster frequencies.

Method—Seven subjects were studied in a total of 14 experiments. Electroencephalograms were obtained

short (five to ten minute) and during lon₁ (seven to eight hour) exposures, although witl the longer period the changes were less obviou in 3 instances, owing to a fall in blood suga₁ duiing that period. When, as an additiona control, compressed air was substituted for 10(per cent oxygen, there was no effect on the fre quency spectrums. The close similarity betweei the frequency specti ums obtained at the start o the experiment and those obtained during th₁ inhalation of air through the mask provides a₁ incidental check on the accuracy of the analyti₁

TABLE 3 —*Effect of Changes in Posture on Frequency Spectiums in the Electroencephalogram*

Subject	Position of Subject	Blood Pressure	\multicolumn{8}{c}{Electroencephalographic Frequency Spectrums, Percentage}	Blood Sugar, Mg. per 100 Cc
			LVF	12/Sec	11/Sec.	10/Sec	9/Sec	8/Sec	7/Sec.	6/Sec	Alpha Activity (8 12/Sec)	
G E Age. 28	Recumbent	114/ 64	3		..	30	52	14	..	..	97	104
	Erect, 15 min	120/ 70	5		2	32	45	15	..	.	..	104
	Recumbent	104/ 70	5		..	19	47	25	4	..	91	91
	Erect, 17 min	. 108/ 80	3		2	22	43	28	3	..	94	91
	Recumbent	106/ 66	..		1	31	47	20	1	..	99	103
	Erect, 8 min	112/ 78	2		3	33	57	23	2	..	96	103
E B F Age: 37	Recumbent	. 115/ 80	..		2	12	34	42	10	..	90	100
	Erect, 17 min	. 126/100	..		2	11	35	42	9	1	90	100
	Recumbent	108/ 80	9	.	..	10	31	40	8	2	81	96
	Erect, 5 min	116/ 94	..	.	..	9	27	49	19	..	85	96
	Recumbent..	. 108/ 88	3		1	15	34	36	10	1	86	95
	Erect, 12 min	118/ 94	1		..	7	46	36	9	1	89	95
J. R Age: 33	Recumbent	. 120/ 85	5	.	1	16	59	18	1	..	94	87
	Erect, 14 min	108/ 70	4	..	.	15	65	14	1	..	94	87
L S Age 32	Recumbent.	. 120/ 82	15	6	35	33	10	1	..	..	85	.
	Erect, 13 min	. 134/ 98	14	2	46	35	3	.	..	.	..	..
M. A. B Age: 57	Recumbent	. 126/ 80	40	8	20	23	8	1	..	..	60	81
	Erect, 14 min	122/ 85	45	5	17	23	9	1	..	..	55	81
R McM. Age: 25	Recumbent	130/ 90	89	2	3	2	4	..	..	..	11	77
	Erect, 10 min	. 118/ 92	91	3	2	1	3	..	..	..	9	77
H W R Age. 29	Recumbent	106/ 56	68	1	4	12	7	5	3	..	29	..
	Erect, 20 min	108/ 75	68	3	1	7	11	7	3	..	29	..

before, during and sometimes after the administration of 100 per cent oxygen by means of a Bulbulian type 14 demand mask modified for constant flow. Oxygen was supplied in excessive amounts, sufficient to keep the reservoir bag well distended at the height of inspiration. As an additional control, air, supplied from a tank of compressed air, was used instead of oxygen in 3 experiments. The duration of most experiments was only fifteen to twenty minutes, not long enough for any significant change in the level of the blood sugar. Six subjects were exposed to an atmosphere of 100 per cent oxygen for a total of seven to eight hours.

Results.—Inhalation of 100 per cent oxygen results in a slight, but significant, shift toward faster rhythms in the cortical frequency spectrums. This was most obvious in the records with regular, dominant alpha activity, but a trend was also present in the records with poor alpha activity. This effect was observed both during

method in the regular, dominant alpha records (fig. 2 C).

Comment.—No studies of the gas content of arterial blood weie carried out on these subjects. However, from other observations it is known that the inhalation of 100 per cent oxygen raises the oxygen saturation of arterial blood to 100 or 105 per cent, the supernormal figure being due to saturation of the plasma with oxygen. It cannot be established from these observations whether the effects noted are due to the increased oxygen tension itself or to changes in the carbon dioxide tension around the cortical cells, since the ability of the capillary blood to take up carbon dioxide is somewhat diminished in the presence of higher oxygen saturation of arterial blood. Whatever the mechanism, these data

again illustrate the readiness with which the electrical activity of the brain responds to alterations in environment of physiologic magnitude.

EFFECTS OF CHANGES IN POSTURE

Seven subjects were studied in 11 observations on the tilt table. There was no difference in the cortical frequency spectrum when the subject was in the erect position and when he was recumbent as long as the blood pressure remained essentially unchanged. The changes associated with orthostatic hypotension are described elsewhere.[8] The absence of any effect of change in posture on the resting electroencephalogram was expected and contrasted with the pronounced effect of changes in posture during hyperventilation.

The data present in table 3 give further evidence of the reproducibility of frequency spectrums in the same person at similar levels of the blood sugar.

HYPERVENTILATION

Hyperventilation is routinely used by most electroencephalographers as a diagnostic aid, but there is considerable disagreement as to the limits of the normal reaction. Only the appearance of the wave and spike pattern is regarded as abnormal by some observers, while others consider as abnormal any appreciable amount of high voltage slow waves of a frequency less than 5 per second. Further, in clinical studies at least, it is impossible to standardize intensity, and sometimes even duration, of hyperventilation because of difficulty in cooperation. An assay of the magnitude of response to ordinary physiologic variables is thus of considerable importance in establishment of criteria of normality.

Blood Sugar.—Variations in the level of blood sugar have been found to influence significantly the appearance of slow waves during hyperventilation.[9] The results of quantitative studies of the magnitude of this effect through a wide range of blood sugar levels and its correlation with changes in acid-base balance in arterial blood are not yet available. Nine of the subjects for whom data are listed in table 1 were studied during the dextrose tolerance tests, the technic of which has

already been described. In table 1 are indicated the prehyperventilation frequency spectrums for each level of the blood sugar. The data for hyperventilation are present in table 4. All examinations were carried out with the subject in the recumbent position. Blood was taken from the femoral artery just before hyperventilation and, again, during the last minute of hyperventilation. Withdrawal of the samples usually took about thirty seconds. For the second sample the electroencephalograph operator signaled at the appearance of sustained large slow waves, or at the end of one hundred and fifty seconds if no large slow waves had appeared by that time. The samples of arterial blood were analyzed for the oxygen content, the carbon dioxide content and the p_H. From 3 subjects samples were obtained in the fasting state and two and a half hours after the infusion; from 6 subjects the first sample was drawn at the end of the infusion and the second two and a half hours later. All subjects hyperventilated as vigorously as possible for one hundred and eighty seconds, but in many instances there were unavoidable variations, usually due to alteration in awareness during the height of the reaction.

The results, presented in table 4, may be summarized as follows:

1. The amount of slowing in the electroencephalogram on hyperventilation tended to vary inversely with the level of the blood sugar after the infusion of dextrose (fig. 2 B). The blood sugar was not the sole determining factor, however, for when the results were listed in order of increasing blood sugar levels, the response during the fasting state was found to be slightly inconsistent in 7 instances (less slowing in 5 and more slowing in 2) as compared with the frequencies at similar levels of the blood sugar in the postinfusion state. This series is too small to establish whether these inconsistencies were due to variations in respiratory exchange during hyperventilation at different times or whether the fasting state differed in some other respect from the postinfusion state at comparable levels of the blood sugar.

2. The intravenous infusion of dextrose in itself did not appear to influence the magnitude of the change in acid-base balance resulting from hyperventilation.

3. With high levels of the blood sugar even maximal shifts in the acid-base balance of arterial blood resulted in only minor changes in distribution of frequencies. Conversely, with low levels of the blood sugar a much smaller shift in the acid-base balance sufficed to bring out significant slowing.

8. Engel, G. L.; Romano, J., and McLin, T. R.: Vasodepressor and Carotid Sinus Syncope: Clinical, Electroencephalographic and Electrocardiographic Observations, Arch. Int. Med., to be published.

9. Engel, G. L., and Margolin, S.: Clinical Correlation of the Electroencephalogram with Carbohydrate Metabolism, Arch. Neurol. & Psychiat. 45:890 (May) 1941. Davis, H., and Wallace, W.: Factors Affecting Changes Produced in the Electroencephalogram by Standardized Hyperventilation, ibid. 47:606 (April) 1942.

TABLE 4.—*Effect of Hyperventilation at Varying Levels of the Blood Sugar on Frequency Spectrums in the Electroencephalogram* *

Subject	Time After Infusion	Status	Period of Hyperventilation Preceding Arterial Puncture, Min.	Arterial Blood						Electroencephalographic Frequency Spectrum (180 Sec. of Hyperventilation), Percentage													
				Carbon Dioxide Content, Vol.%	Carbon Dioxide Combining Power, Mm.Hg	(BHCO$_3$)	pH	Oxygen Tension, Vol.%	Blood Sugar, Mg. per 100 Cc.	LVF	12/Sec.	11/Sec.	10/Sec.	9/Sec.	8/Sec.	7/Sec.	6/Sec.	5/Sec.	4/Sec.	3/Sec.	2/Sec.	1/Sec.	Alpha Activity (8–12/Sec.)
E. B. F. Age: 37	2½ hr.	Resting	170	42.9	38	23.5	7.41‖	19.3	72	1	…	…	7	17	22	27	13	7	3	2	…	…	47
		HV	…	33.0	13?	19.7?	7.8?	20.6	72	1	…	1	6	13	25	28	15	7	3	1	…	…	45
	2 hr.	HV	…	43.4	38	24	7.42	19.0	95	5	1	…	6	28	20	17	0	…	…	…	…	…	72
	Fasting	HV	200	32.2	17	18.8	7.66	20.1	101	1	…	…	7	33	36	18	5	…	…	…	…	…	76
	1 hr.	HV	…	…	…	…	…	…	101	1	…	2	19	43	27	7	1	…	…	…	…	…	91
	End of Infusion	HV	…	…	…	…	…	…	385	2	…	2	19	43	27	7	1	…	…	…	…	…	91
G. E. Age: 28	2 hr.	Resting	…	47.7	41	25.5	7.41	18.0	72	…	…	…	5	17	17	15	13	10	7	11	5	…	30
	2½ hr.	HV	120	35.5	16.5	20.5	7.71	18.6	76	…	…	…	4	16	17	10	10	7	10	17	8	…	37
	Fasting	HV	120	44.1	37	24.0	7.43	18.2	86	…	…	…	9	32	40	14	5	1	…	…	…	…	81
	1 hr.	HV	…	37.2	21.5	21.0	7.60	18.6	120	…	…	…	10	44	31	13	2	…	…	…	…	…	85
	End of Infusion	HV	…	…	…	…	…	…	…	…	…	2	13	47	31	6	…	…	…	…	…	…	91
J. R. Age: 31	2½ hr.	Resting	160	46.1	42	25	7.39	18.7	76	…	…	…	2	6	16	16	27	18	8	6	…	…	21
	2 hr.	HV	…	31.7	16	19.3	7.69	19.8	79	1	…	…	6	26	23	24	17	3	…	…	…	…	55
	Fasting	HV	180	45.3	46	24	7.33	17.7	100	2	…	…	10	44	20	16	7	1	…	…	…	…	74
	1 hr.	HV	…	35.4	18	20	7.66	19.0	122	…	…	…	8	27	42	17	6	…	…	…	…	…	77
	End of Infusion	HV	…	…	…	…	…	…	342	…	…	…	11	55	22	6	2	…	…	…	…	…	91
L. S. Age: 32	3 hr.	Resting	130	47.9	37	26.5	7.47	20.0	81	10	…	6	14	21	7	14	7	10	7	3	…	…	48
	2½ hr.	HV	…	35.1	16	20	7.71	21.0	85	11	1	7	21	15	12	13	12	7	2	…	…	…	56
	2 hr.	HV	…	…	…	…	…	…	109	15	2	16	45	18	4	…	…	…	…	…	…	…	85
	Fasting	HV	…	…	…	…	…	…	127	14	…	6	35	27	16	3	…	…	…	…	…	…	83
	1 hr.	HV	…	…	…	…	…	…	195	10	4	29	30	16	6	…	…	…	…	…	…	…	90
	End of Infusion	Resting	100	47.0	45	25	7.36	19.1	303	15	5	22	31	21	6	…	…	…	…	…	…	…	85
		HV	…	34.5	17	19.5	7.66	19.5	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…

142

Table continued — EEG and blood chemistry values for the subjects listed by increasing blood sugar level.

Subject	Time	Line	Note / min. HV	—	—	—	—	pH	—	Blood sugar	EEG / wave counts (left → right)
J. McM. Age: 26	2½ hr	Resting	Onset of 2-5/Sec. waves after 120 min. of HV	45.5	36	25	20.0	7.46	20.0	83	8 .. .. 6 8 15 12 8 13 11 11 15 5 .. 29
		HV		32.7	20	18.5	21.6	7.58	21.6	90	2 .. .. 7 16 11 21 14 11 10 20 33 37
	2 hr	HV		....	....	....	....	....	....	103	6 .. .. 8 15 20 7 11 10 8 15 11 3 .. 43
	1 hr	HV		....	....	....	....	....	....	107	12 .. .. 3 8 9 5 7 18 8 9 1 21
	Fasting	HV		....	....	....	....	....	....		9 1 33 25 18 1 ..
	End of infusion	Resting		43.8	38	21	20.5	7.41	20.5	210	12 1 13 .. 25 18 9 .. ..
		HV	140	27.3	11	16	21.0	7.77	21.0		
M. A. B. Age: 57	2½ hr	Resting	Onset of 2-5/Sec. waves after 100 min. of HV	47.9	37	26	18.4	7.46	18.4	81	30 .. 2 .. 7 1 13 9 16 11 6 7 2 ..
		HV		33.0	14	18.5	19.4	7.74	19.4		
	Fasting	HV		....	....	....	....	....	....	91	24 1 2 20 24 1 6 4 11 7 ..
	2 hr	HV		....	....	....	....	....	....	93	11 9 .. 9 9 9 7 14 6 8 2 ..
	1 hr	HV		....	....	....	....	....	....	107	9 15 3 27 11 15 5 ..
	End of infusion	Resting		49.0	41	26	17.8	7.42	17.8	215	51 23 2 17 4 3 23 ..
		HV	180	34.4	14	19.5	18.4	7.75	18.4		
J. P. W. Age: 29	2 hr	HV†		....	....	....	....	....	....	70	32 2 11 18 16 12 .. 4 ..
	2½ hr	Resting		44.5	37	21	18.8	7.42	18.8	83	28 .. 8 14 11 4 6 8 11 5 ..
		HV	150	31.7	15	18.5	19.4	7.70	19.4		
	Fasting	HV		....	....	....	....	....	....	95	13 .. 4 19 30 17 4 7 2 2 ..
	1 hr	HV		....	....	....	....	....	....	103	23 .. 4 12 16 21 4 9 4 4 ..
	End of infusion	Resting		44.8	44	24	18.3	7.35	18.3	205	35 8 17 24 11 .. 17 ..
		HV	150	34.2	20	19	19.0	7.75	19.0		
H. W. R. Age: 29	1 hr	HV		....	....	....	....	....	....	70	8 .. 3 3 11 16 11 7 9 ..
	2 hr	HV		....	....	....	....	....	....	76	9 .. 2 2 9 11 12 6 15 3
	2½ hr	Resting		48.6	39	29.5	15.4	7.43	15.4	82	8 .. 4 8 9 8 8 9 16 13 2
		HV	120	36.6	19	20.5	16.5	7.65	16.5		
	Fasting	HV		....	....	....	....	....	....	93	2 1 7 14 7 11 2 15 18 8
	End of infusion	Resting		48.5	46	25	16.3	7.35	16.3	163	4 1 4 11 18 24 20 4 2
		HV	140	33.6	17	18.5	16.5	7.65	16.5		
R. McM. Age: 25	2½ hr	Resting		45.0	39	29.5	21.7	7.38	21.7	76	26 5 3 10 9 3 9 13 11 8 1
		HV	100	30.9	19	22.2	22.2	7.69	22.2		
	2 hr	HV		....	....	....	....	....	....	82	31 3 7 16 11 4 1 3
	Fasting	HV		....	....	....	....	....	....	95	40 16 10 10 3 18
	1 hr	HV		....	....	....	....	....	....	131	39 11 8 10 5 8
	End of infusion	Resting		43.5	46	25	20.2	7.40	20.2	289	49 22 10 6 1 12
		HV	160	29.0	17	18.5	21.0	7.57	21.0		

* Values are listed in order of increasing blood sugar levels. The subjects and the values obtained in the dextrose tolerance tests are the same as those indicated in table 1.

† In this column, HV indicates hyperventilation.

‡ BHCO₃ indicates base bicarbonate.

¶ The hyperventilation was poorly done.

‖ The p_H buffer solution used in this instance did check on control determination.

The hematocrit reading was 55 per cent.

143

4. Disturbances in consciousness tended to correlate with the amount of slow activity and were greatest at low levels of the blood sugar. On the other hand, the subjective symptoms of numbness, tingling and the like, if different at all, were greater at the higher levels of the blood sugar.

Comment.—Blood sugar levels are obviously of the greatest importance in determination of the response of the electroencephalogram to hyperventilation. The mechanism of this action is not clarified by these studies and must await corresponding work on the cerebral blood flow and changes in the oxygen and carbon dioxide contents of arterial and internal jugular venous blood at varying levels of the blood sugar. It is apparent that the electroencephalographic changes are not due to any effect that the changing level of the blood sugar has on the degree of respiratory alkalosis provoked by hyperventilation.

In blood sugar during hyperventilation, it is our opinion that while the wave and spike pattern may be considered defintely abnormal, 3 to 5 per second activity may be regarded only as probably abnormal when the blood sugar is above 120 mg. per hundred cubic centimeters and of doubtful significance at lower levels. Age must also be taken into account, since Liberson and Strauss [10] demonstrated that the amount of slow cerebral activity on hyperventilation varies inversely with age.

TABLE 5.—*Effect of Hyperventilation in the Recumbent and the Erect Position on Frequency Spectrums in the Electroencephalogram*

Subject	Blood Sugar, Mg. per 100 Cc.	Position of Subject	Blood Pressure	Pulse Rate	LVF	12/ Sec.	11/ Sec.	10/ Sec.	9/ Sec.	8/ Sec.	7/ Sec.	6/ Sec.	5/ Sec.	4/ Sec.	3/ Sec.	2/ Sec.	1/ Sec.	Alpha Activity (8-12/Sec.)
G. E. Age: 28	104	Recumbent	112/ 68	114	2	..	..	8	19	28	16	8	5	5	6	2	..	55
		Erect, 22 min.	98/ ?	150	1	..	..		14	16	18	11	16	13	8	3	..	30
	91	Recumbent	116/ 68	114	2	..	..	3	19	16	8	10	13	11	12	6	..	38
		Erect, 24 min.	112/ 90	114	..	..	..	2	9	9	14	11	13	14	18	10	..	20
	103	Recumbent	114/ 68	90	..	..	..	6	14	24	15	12	11	6	9	2	..	44
		Erect, 20 min.	120/ 70	114	..	..	..	4	10	14	16	12	13	9	14	7	..	28
E. B. F. Age: 37	100	Recumbent	120/ 86	114	2	..	..	5	17	36	15	13	7	3	2	..	..	58
		Erect, 30 min.	116/ 84	138	2	..	..	3	9	23	21	12	9	6	12	2	..	35
J. R. Age: 34	87	Recumbent	125/ 80	90	4	..	..	10	40	11	9	11	9	4	2	..	..	61
		Erect, 18 min.	95/ 80	102	2	..	..	6	25	16	6	8	10	16	7	5	..	47
L. S. Age: 32	122	Recumbent	110/ 80	96	11	4	27	36	19	2	1	..	..	..	..	..	..	88
		Erect, 22 min.	134/ 84	132	20	3	19	23	11	11	9	3	1	..	..	..	..	67
M. A. B. Age: 57	81	Recumbent	121/ 80	90	12	3	6	13	9	6	11	14	18	7	..	..	..	37
		Erect, 21 min.	86/ 56	132	10	..	6	11	14	7	11	12	17	9	3	..	..	38
R. McM. Age: 26	77	Recumbent	120/100	90	30	6	5	5	3	4	8	7	10	13	7	2	..	23
		Erect, 13 min.	122/104	114	35	..	2	4	8	3	8	13	7	9	8	2	..	17
H. R. Age: 29	?	Recumbent	108/ 56	78	16	9	10	23	12	12	10	3	3	4	2	1	..	61
		Erect, 18 min.	118/ 80	90	9	1	1	4	6	8	10	8	14	9	13	14	1	20
J. McM. Age: 26	87	Recumbent	140/ 90	126	3	..	3	18	9	9	9	4	11	12	15	6	..	41
		Erect, 24 min.	130/ 90	132	9	..	2	11	7	3	7	13	16	17	11	3	..	23
R. A. K. Age: 42	105	Recumbent	142/ 90	114	38	..	2	10	20	16	9	3	..	2	..	..	..	48
		Erect, 28 min.	95/ 80	150	8	..	1	5	3	4	8	9	16	27	16	2	..	13

In routine clinical work, caution must be observed in the interpretation of slowing of cerebral activity during hyperventilation if the level of the blood sugar is not known. Until further data are available on the response of the abnormal electroencephalogram to variations

As for experimental work, it need only be stated that observations during hyperventilation are without significance unless the factor of the level of blood sugar is controlled.

Posture.—Nine subjects were studied on the tilt table. After they had recovered from three minutes of vigorous hyperventilation in the recumbent position, they were tilted to the erect position, and after thirteen to thirty minutes of motionless standing, they again overventilated

10. Liberson, W. T., and Strauss, H.: Electroencephalographic Studies: Slow Activity During Hyperventilation in Relation to Age, Proc. Soc. Exper. Biol. & Med. **48:**674, 1941.

for three minutes. One channel was used to record the electrocardiogram. The blood pressure was determined frequently before and during hyperventilation. In no instance was there a significant fall in arterial blood pressure due to motionless standing alone.

In all but 2 instances the degree of slowing of the brain waves was significantly greater when the subject was in the erect position than when he was in the recumbent position (table 5; fig. 2 D). In a few subjects the difference was striking. In all instances hyperventilation was accompanied by tachycardia, which was always greater when the subject was in the erect position. During hyperventilation there were usually a slight decrease in pulse pressure with the subject in the recumbent position and a more decided decrease when he was in the erect position. In 4 instances the systolic pressure fell to below 100 mm. of mercury. Disturbances in consciousness were greater with the subject in the standing position, but in no instance did muscular relaxation or evidences of impending syncope develop. Three subjects, not included in the present series, hyperventilated first in the erect and then in the recumbent position, with similar results; this observation rules out the possibility that the greater effect noted when the subject was in the erect position was due to incomplete recovery from the first period of hyperventilation.

Comment.—The most obvious physiologic difference in response to hyperventilation in the two positions is found in the magnitude of the circulatory reactions. Cerebral blood flow is known to decrease when the subject hyperventilates in the recumbent position. The magnitude and direction of the observed changes in pulse and blood pressures when the subject is in the erect position are such as to suggest that if any further change in cerebral blood flow is associated with the erect position, it is in the direction of an additional decrease. This circulatory reaction, however, is not the only factor, or even necessarily the most important one, since the degree of change in the electroencephalogram did not correlate well with the magnitude of the changes in the pulse and blood pressures. Indeed, in the instance in which the blood pressure fell to the lowest point the cortical frequency spectrum showed the least change. Another possible factor may be a more effective respiratory exchange when the subject is hyperventilating in the erect position, due to a greater vital capacity. Whatever the mechanism, the results make it clear that posture must be taken into account as a variable in both clinical and experimental studies involving hyperventilation.

GENERAL COMMENT

The method of analysis of cortical frequency spectrums presented in this report provides a simple and practical procedure for quantitating changes in frequency under varying experimental conditions. The method, however, has certain limitations, which must be emphasized. First, as has already been pointed out, the distribution of waves per second, rather than the distribution of wavelengths, is determined. For this reason, waves of certain lengths which are obvious on inspection of the record but which appear in runs of less than one second's duration may not be represented in the spectrum, since they are averaged with waves of the more dominant frequency. While these spectrums are thus not strictly comparable to spectrums for true wavelengths, they are nevertheless of equal value in demonstrating shifts in frequency. In this respect studies using this method and those employing the Grass analyzer[2] have yielded comparable results.

A second criticism is that our method represents an oversimplification of the electroencephalogram in that it ignores the subdominant superimposed and base line oscillations. This need not be a serious obstacle to the detection of significant shifts in frequency, since the results with the Grass analyzer have indicated that while the electrical activity of the cortex is a manifestation of the activity of a great number of chemical oscillators having different natural periods, these oscillators tend to respond to the same factors in the same direction, though not necessarily to the same degree. The present method depends chiefly on the oscillators, which are represented by sine waves to a greater or less degree. Analysis of normal records containing only a small proportion of sine wave activity (i. e., low voltage fast waves or low alpha rhythm) proves difficult during variations within physiologic ranges, but in their shift to abnormal zones there is usually an increase in sine wave activity of slower frequency. This has been demonstrated in studies on delirium,[6] during hyperventilation and during exposure to toxic substances.[11] For the study of borderline changes in normal subjects, however, it is probably advisable to select subjects whose electroencephalograms have a high percentage of alpha activity.

With respect to the influence of various constituents of the blood, our studies confirm Gibbs's data indicating that at least the distribution of frequencies shows a continuous change through normal and supernormal ranges, as well as in

11. Unpublished data.

pathologic ranges.[2] The normal electroencephalogram thus reveals a considerable range in distribution of frequencies within physiologic zones. This observation offers a new approach to the study of the abnormal, and more particularly the borderline normal, electroencephalogram, especially when disturbances in cerebral metabolism may be present. This is of particular value in studies of toxic substances or noxious procedures, in which it is of importance to detect the earliest harmful effects on the central nervous system. By establishing the normal zones of response to physiologic variables in the experimental subjects (fig. 2) one can more readily detect the point at which the noxious experience exceeds the physiologic zone for each subject. It is obvious from the data in this paper alone that the mere presence or absence of delta activity is not an adequate criterion. When the technic is combined with careful psychologic studies of fluctuations in the level of awareness, one has no difficulty in establishing with a high degree of accuracy normal, borderline and pathologic zones. So far we have used this technic successfully in investigations on a number of harmful materials, including alcohol, and on oxygen lack, as well as in a study of clinical delirium due to a wide variety of factors.[3]

SUMMARY

A simple method of determination of the average frequency distribution of the electroencephalogram, which is presented here, yields a spectrum of the average number of waves per second and is highly accurate for regular records, although progressively less accurate with records of decreasing regularity.

After intravenous infusion of dextrose there was a shift toward faster frequencies (up to 12 per second) with rising levels of dextrose in the blood and a shift toward slower frequencies with falling levels of dextrose. The amount of low voltage fast activity, however, was not influenced by the dextrose level in the blood.

Inhalation of 100 per cent oxygen for five minutes or longer resulted in a shift toward faster frequencies (up to 12 per second).

Change from the recumbent to the erect posture had no effect on the cortical frequency spectrum unless orthostatic hypotension developed.

The decrease in frequency of the brain waves during hyperventilation was greatest with low dextrose levels in the blood and least with high dextrose levels in the blood, in spite of comparable alterations in hydrogen ion concentration, carbon dioxide tension, carbon dioxide content and base bicarbonate concentration of the arterial blood.

Hyperventilation produced much greater slowing when the patient was in the erect position than when he was in the recumbent position. Tachycardia and decrease in pulse pressure were also greater when the subject was in the erect position than when he was in the recumbent position during hyperventilation.

Cincinnati General Hospital.

ELECTRODIAGNOSIS BY MEANS OF PROGRESSIVE CURRENTS OF LONG DURATION

STUDIES ON CATS WITH EXPERIMENTALLY PRODUCED SECTION OF THE SCIATIC NERVES

LEWIS J. POLLOCK, M.D.; JAMES G. GOLSETH, M.D.; ALEX J. ARIEFF, M.D.; IRVING C. SHERMAN, M.D.; MAURICE A. SCHILLER, M.D., AND ELI L. TIGAY, M.D.

CHICAGO

In his description of the reaction of degeneration, Erb[1] included as a part of the changes the increase in galvanic excitability. This was a subject of dispute between Vulpian and Erb and Biedermann and Erb.

Erb stated that there was an invariable increase in galvanic excitability, beginning in the second week and lasting as long as two months. Roberts,[2] in experiments on rabbits in which the bare muscle was stimulated, found this to be a constant sign; "about three weeks after nerve section the increased response to the galvanic current . . . is indeed very striking." In his experience in clinical work the results obtained were less constant.

Employing percutaneous bipolar stimulation, we have found that two weeks after section of the sciatic nerve in the cat the liminal amount of current is small, usually below 1 milliampere —at times of the order necessary to stimulate the normal muscle but frequently less. In our experiments the first electrical examination was made fourteen days after section to prevent injury to the degenerating muscles.

This low threshold for galvanic stimulation persists for a long time. In completely denervated muscles, large portions of the sciatic nerve having been removed and absolute alcohol having been injected into the proximal and distal ends to discourage regeneration, we observed this low threshold to persist as long as our experiments were continued, for two hundred and eighty-two days (fig. 1). In animals in which the sciatic nerves were sectioned and the ends looped back and sixty days later the ends resected and sutured, we also noted this low threshold to galvanic stimulation during the sixty days preceding secondary suture. In animals in which the sciatic nerves were sectioned and the ends immediately sutured, we observed the same lowered threshold to galvanic stimulation for a certain number of days, varying from thirty-seven to sixty, when, either before or coincident with motor signs of recovery, the minimal amount of current necessary to produce a contraction suddenly increased and diminished only later, remaining high for as long as one hundred and twenty days (fig. 2).

We wish here to call attention to the confirmation of Erb's observation of the existence of a low threshold of excitability to galvanic stimuli after complete section of a nerve and to its persistence for as long as our denervated animals were observed, two hundred and eighty-two days. We particularly wish to mention the sudden increase in the threshold to galvanic stimulation immediately before, and at times just when, motor signs of successful neurotization occur. We call attention to this increase since a related phenomenon in the response of denervated muscles to progressive currents has been described and is confirmed by us, and since in cats at least positive indication of successful neurotization may be obtained by means of such currents.

The relation existing between the rate of variation in current and the minimal strength of current required to produce excitation has been investigated by physiologists for many years, since an attempt was made to study it by Du Bois-Reymond[3] in 1862. Bernstein,[4] von Fleischl,[5] von Kries,[6] Fick,[7] Schott[8] and Gildemeister[9] were among the older investigators.

1. Erb, W.: Deutsches Arch. f. klin. Med. 4:535-578, 1868.

2. Roberts, F.: Brain 39:297-347, 1916.

3. Du Bois-Reymond, E.: Abhandl. d. k. Akad. d. Wissensch. zu Berlin, 1862, pp. 75-163.

4. Bernstein, J.: Arch. f. Physiol., 1862, pp. 531-532.

5. von Fleischl, E.: Sitzungsb. d. k. Akad. d. Wissensch. Math.-Naturw. cl. 76:138-162, 1877.

6. von Kries, J.: Arch. f. Physiol. 8:337-372, 1884.

7. Fick, A.: Beiträge zur vergleichenden Physiologie der irritabelen Substanzen, Braunschweig, F. Vieweg u. Sohn, 1863.

8. Schott, J.: Arch. f. d. ges. Physiol. 48:354-385, 1891.

147

Such so-called progressive currents as have been studied may be divided into linearly increasing, or progressive, currents and exponentially increasing, or progressive, currents.

Among the more recent investigators to whom more accurate methods of measurement have been available and who have studied exponentially rising currents may be mentioned Liberson,[10] Schriever,[11] Delville,[12] Cardot and Laugier,[13] d'Hollander,[14] Solandt[15] and Fabre.[16] In these experiments the duration of rise of the exponentially increasing current to its peak was less than one second—often fifty to two hundred

one second—in the case of Lucas [17] one and two-tenths seconds. From these experiments certain predictions were made in relation to the response of muscle and nerve to progressive currents of long duration which have not been confirmed by our work. Certain formulas and constants have been derived from the experiments with currents of relatively short duration which we feel will require some modification, but with which we are not concerned at this time. In 1907 Lucas published the results of his studies on the sciatic nerves of the toad and frog and on the sartorius muscle of the frog. He
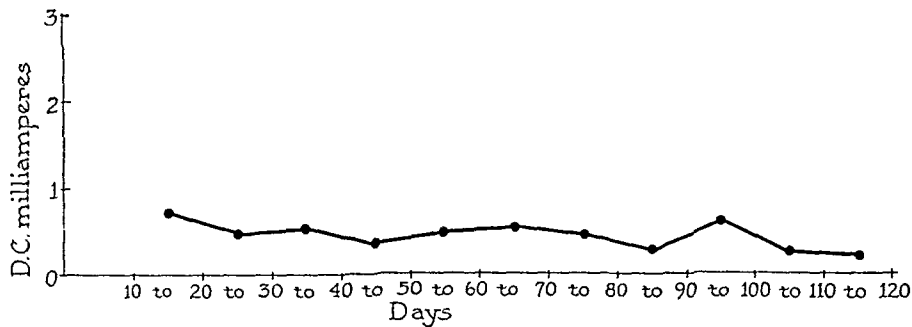
Fig. 1.—Average milliamperage necessary to produce an adequate stimulus by bipolar anodal closing stimulation at various days after denervation.
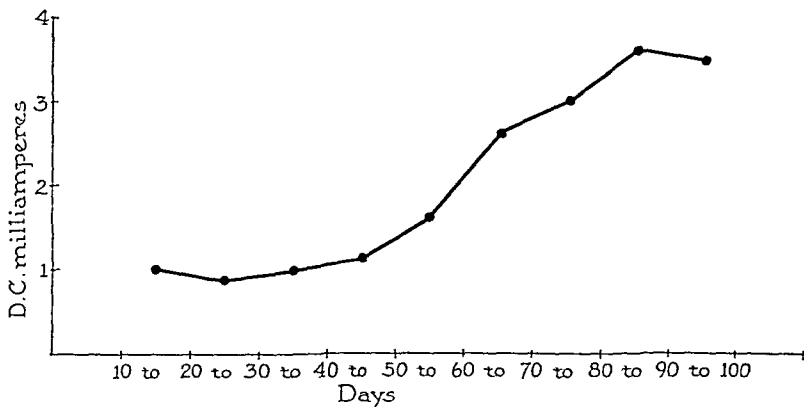
Fig. 2.—Average milliamperages necessary to produce an adequate stimulus by unipolar anodal closing stimulation at various days after primary suture.

milliseconds. In the more recent experiments on linearly increasing, or progressive, currents, the longest period likewise was usually less than

9. Gildemeister, M.: Arch. f. d. ges. Physiol. **101**: 203-225, 1904.

10. Liberson, W.: Compt. rend. Soc. de biol. **116**: 1319-1322, 1934.

11. Schriever, H.: Ztschr. f. Biol. **91**:173-195, 1931.

12. Delville, P.: Arch. internat. de physiol. **40**:83-128, 1934.

13. Cardot, H., and Laugier, H.: J. de physiol. et de path. gén. **15**:1134-1147, 1913.

14. d'Hollander, L.: Arch. internat. de physiol. **51**: 299-329, 1941.

15. Solandt, D. Y.: Proc. Roy. Soc., London, s.B **119**:355-379, 1936.

16. Fabre, P.: Compt. rend. Acad. d. sc. **185**:300-302, 1927.

found that the minimal rate of rise, which he called the minimal current gradient, in the case of the toad was of such an order that the liminal strength at instantaneous stimulation would have to be increased 46 times at the end of a second to produce an effective stimulus; for the sciatic nerve of a frog, the minimal strength at instantaneous stimulation would have to be increased 63 times at the end of a second to be an effective stimulus. Among his conclusions is the following statement:

It is found that as current gradient is decreased the current strength required for excitation increases more and more rapidly until a definite minimal gradient is reached. No gradient less steep than this will excite.

17. Lucas, K.: J. Physiol. **36**:253-274, 1907-1908.

The belief that progressive currents possessing less than a minimal rate of rise will not stimulate even though they finally reach a considerable value was likewise expressed by Hill.[18] From Lucas' experiments, Blair[19] reached the conclusion that "when the gradient is too low for the rheobase to be effective no voltage is effective."

In an analysis of Solandt's[20] data obtained from stimulation of the frog's sciatic nerve with exponentially rising currents, it may be seen that with a minimal gradient the current increases at a rate such that a value 16.7 times the rheobase value is reached in 0.27 second.

We found when using linearly increasing currents of longer duration—1.2, 2.6, 3.8 and 8.8 seconds—that the aforementioned liminal gradients did not exist for all times. One graph (fig. 3) may suffice to illustrate the point. In the case of the normal muscle, the liminal current

long as the current is allowed to increase progressively at that particular rate of change. While we shall postpone our explanation of these observations until a later communication, we wish to report on the differences observed in completely denervated muscle, recovering muscle and normal muscle.

Electrodiagnosis and electrotherapy by means of currents having various wave forms have been studied for many years. These studies include investigations on condenser discharges; faradic currents, when applied suddenly and interrupted suddenly, and when applied in a slowly increasing and decreasing wave form, as described by Bergonie[21]; variations of square wave galvanic currents of varying periods, such as the le Duc current, and, finally, unidirectional sinusoidal currents, alternating currents, linearly progressive currents and exponentially increasing cur-
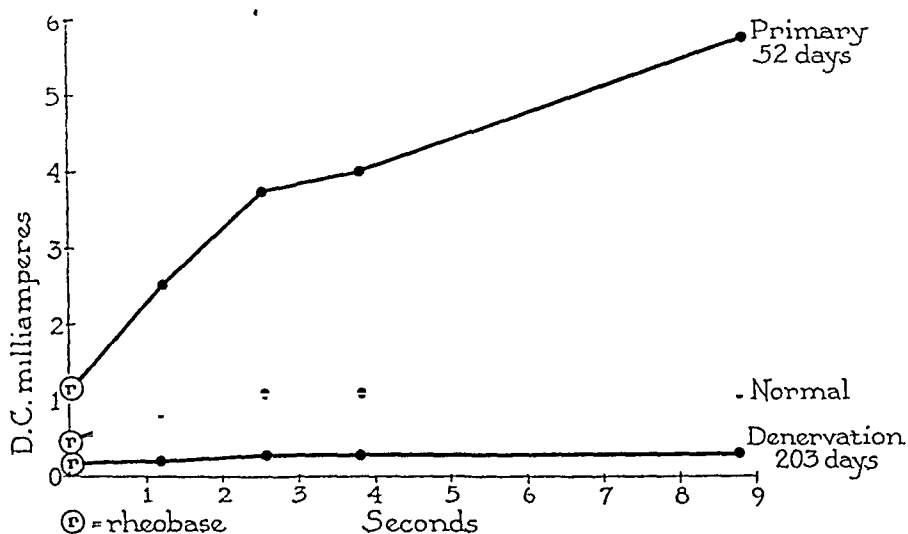
Fig. 3.—Comparison of milliamperages necessary to produce an adequate stimulus with progressive currents of various durations after a primary suture and in a normal and a denervated muscle.

at instantaneous stimulation, or the rheobase, was 0.4 milliampere; at 1.2 seconds the current was 0.8 milliampere, or twice the rheobase; at 2.6 seconds, 1.05 milliamperes, or 2.62 times the rheobase; at 3.8 seconds, 1.1 milliampere, or 2.75 times the rheobase, and at 8.8 seconds, 1.15 milliamperes, or 2.87 times the rheobase. At no time was the rheobasic current adequate to stimulate; yet with a current of long duration, 8.8 seconds, an increase of only 2.87 times the rheobase was an effective stimulus. We observed that there is a relatively liminal gradient for each particular time in which the peak of the current is reached. When at that current gradient a contraction begins at, say, 3.8 seconds and the current is allowed to increase linearly to 8.8 seconds, a tetanic contraction persists as

rents. The last four types of currents are of interest in relation to our work.

In earlier years the impetus for development of new wave forms of stimulation was the desire to imitate the normal contraction of a muscle and to avoid the abrupt movement produced by sudden closure of a current, whether faradic or galvanic (Bergonie). In 1907 Bordet[22] described an apparatus for the production of a galvanic wave current lasting as long as 2.5 seconds. With regard to diagnosis, he noticed that when a muscle is degenerated the time necessary to reach a current adequate for stimulation is long as compared with that necessary for normal muscle, with which the liminal current must be reached more quickly. For similar reasons, Laquerrière[23] designed a new apparatus on the basis of the work of Bergonie. In

18. Hill, A. V.: J. Physiol. 40:190-224, 1910.

19. Blair, H. A.: J. Gen. Physiol. 15:731-755, 1931-1932.

20. Solandt, D. Y.: Proc. Roy. Soc., London, s.B 120::389-408, 1937.

21. Bergonie, J.: Arch. d'électric. méd. 4:66-69, 1896.

22. Bordet, E.: Arch. d'électric. méd. 15:452-461, 1907.

23. Laquerrière, A.: Bull. off. Soc. franç. d'électrothérap. 15:143-154, 1907.

1912 Becker [24] described an apparatus called a myomotor, which delivered saw tooth waves. In 1931 Delherm and Laquerrière [25] described an apparatus which delivered alternating currents of long duration and unidirectional galvanic wave forms. The currents described by Bordet, Laquerrière and Delherm have been designated by Duhem [26] as currents of long period, to distinguish them from currents described by d'Arsonval in 1891 and by Lapicque,[27] who, without knowledge of the work of d'Arsonval,[28] published the results of his studies in 1915.

Whereas the currents designated as those of long period may last several seconds, those designated as progressive currents by Delherm

Although many articles in the literature are concerned with progressive currents of long period (more than two seconds), the clinical material from which data have been obtained is small. No accurate measurements of time and current are described, and no experimental work is recorded.

It is necessary, we believe, better to define a progressive current. We take such a current to be one which increases with time. The kind of progressive current is determined by its wave form—for example, whether linear, exponential or sinusoidal.

The progressive current used in these experiments was a linearly increasing one, consisting
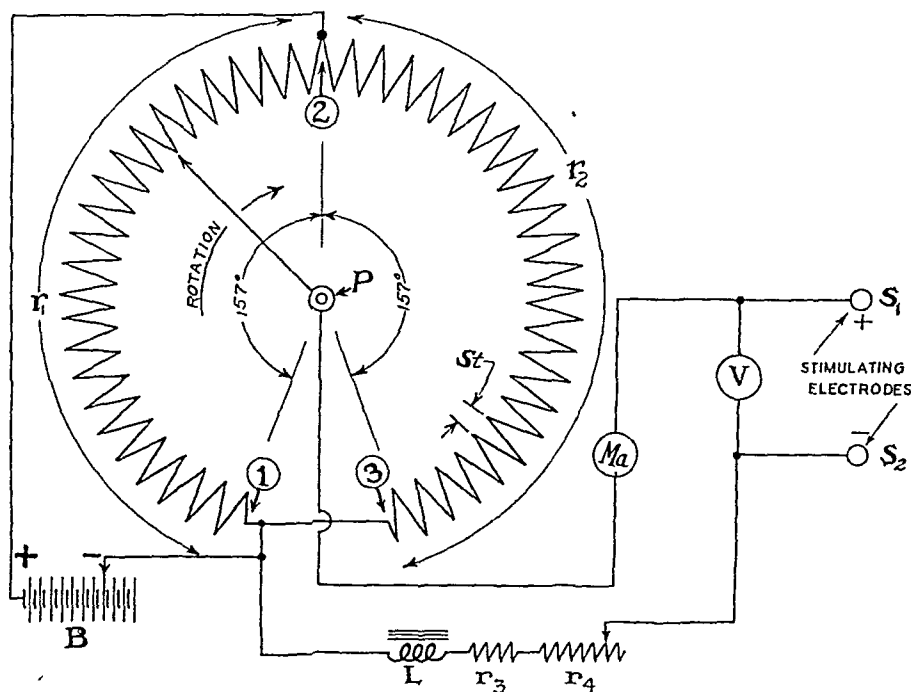
Fig. 4.—Circuit diagram of the apparatus for production of progressive currents.

In this diagram, r_1 and r_2 indicate the potentiometer, with a resistance of 400 ohms; r_3 is the fixed resistor, with a resistance of 1,000 ohms; r_4, the rheostat, with a resistance of 100,000 ohms; L, the choke coil, with an inductance of 30 henrys and a resistance of 130 ohms; St, a step, or the distance between adjacent turns of wire, r_1 and r_2 equaling 600 steps; B, the storage battery; Ma, the milliammeter, and V, the voltmeter, with a resistance of 5×10^6 ohms. All resistors are wound with wire.

last only a fraction of a second. From the standpoint of their contribution to diagnosis, it is said of both types that a degenerated muscle will respond to the condition in which a liminal current is reached more slowly, whereas with the normal muscle this amperage must be reached more quickly.

of the ascending limb of a unidirectional galvanic wave of isosceles triangle type. The decision to use a current wave of this type in preference to a saw tooth wave was based on several considerations. In the first place, one is able to observe a contraction at the peak of the wave. Also, one is able to obtain simultaneous readings of the voltage and strength of current at the instant of the contraction. In addition, one is spared the confusion resulting from unwanted break contractions, which are likely to occur with the saw tooth wave.

The generation of the wave of the isosceles triangle type is dependent on the operation of a specially constructed potentiometer, the moving

24. Becker, W.: Ztschr. f. phys. u. diätet. Therap. **16**:583-600, 1912.

25. Delherm, P., and Laquerrière, A.: Compt. rend. Acad. d. sc. **192**:1766-1767, 1931.

26. Duhem, P.: J. de radiol. et d'electrol. **18**:601-610, 1934.

27. Lapicque, L.: Compt. rend. Acad. d. sc. **161**:643-646, 1915.

28. d'Arsonval, A.: Compt. rend. Soc. de biol. **3**:283-286, 1891.

arm of which may be continuously rotated through multiples of 360 degrees at various predetermined, constant rates. This moving arm is driven through suitable worm and spur gear reduction units by means of a shaded pole, 60 cycle induction motor, the speed of which is held constant by a centrifugal governor. A ripple-free, unidirectional current is supplied to the potentiometer from a low resistance storage battery, the output of which could be varied in 2 volt increments from zero to 36 volts. This primary current enters the center tap (point 2) of the potentiometer winding and passes out through the junction between the initial and the final turn (points *1* and *3*) of this winding (fig. 4).

A secondary current, which shall be called hereafter a progressive current, emerges from the moving arm of the potentiometer and passes through an external series circuit, consisting of a milliammeter, the specimen, a variable resistor, a fixed resistor and a choke coil. The milliam-

Because of the inertia of the galvanometer, there was an appreciable difference between the dynamic and the static values for the current and the voltage at the faster times. For example, at the 1.2 second time the dynamic value of the current was 0.9 milliampere and the static value 1.02 milliamperes. At the 2.6 second time the dynamic value was 1.02 milliamperes and the static value 1.05 milliamperes. At the 3.8 second time the dynamic value was 1.03 milliamperes and the static value 1.05 milliamperes. At the 8.8 second time the dynamic value was 1.05 milliamperes and the static value 1.06 milliamperes. There was a corresponding difference in the dynamic and the static values for the voltage.

Figure 5 shows that 1.1 milliamperes was the average strength of current required to produce a minimal contraction in 25 normal specimens at the 3.8 second time. For a progressive current of this value it was possible to have the total resistance of the external circuit at a value
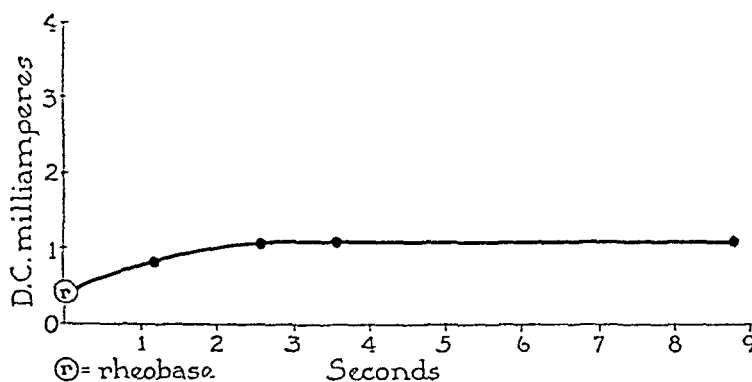
Fig. 5.—Median of the milliamperages necessary to produce an adequate stimulus with progressive currents of various durations in 25 normal animals.

meter has been placed in the circuit to measure the current actually passing through the specimen. Although the voltmeter is located across the stimulating electrodes, the current which passes through it is truly negligible. The variable resistor, r_4, enables one to obtain continuously adjustable maximums of current, from about 0.125 to 15 milliamperes, and it assists in maintenance of linearity in the current wave, though the specimen may be changing in resistance during the examination.

The fixed resistor, r_3, which has a value of 1,000 ohms, is always kept in the circuit to assure linearity, even when r_4 is reduced to a low value. The choke coil is used to smooth out the small, but unavoidable, step effect which is created as the moving arm of the potentiometer passes from one turn of the resistance winding to the adjacent turn.

In this discussion, the terms 1.2, 2.6, 3.8 and 8.8 second times mean that 1.2, 2.6, 3.8 and 8.8 seconds respectively are required for the progressive current to reach its maximal value.

slightly greater than 27,000 ohms. This fact is emphasized because the accompanying cathode ray oscillogram (fig. 6) showed excellent linearity of the wave when the total resistance of the external circuit was only 1,000 ohms and the maximal value of the progressive current was as high as 10 milliamperes.

Before the examination, the site over which the electrodes were to be placed was first pricked deeply by a needle five times and vigorously rubbed with electrode jelly to minimize cutaneous resistance; the indifferent electrode, measuring 2 cm. in diameter, was placed over the lateral portion of the achilles tendon. The exploring electrode, the anode, measuring 1.5 cm. in diameter, was placed in the middle and lower part of the popliteal fossa. The electrodes, which were circular, were constructed of copper and covered with chamois; they were immersed in salt solution for fifteen minutes prior to use and then covered with electrode jelly. When a rheobase was to be determined, the choke coil was shunted out of the circuit.

In addition to studies of linearly increasing progressive currents, we studied the effect of alternating currents and half-wave rectified alternating currents of very low frequencies, 90 degrees of which last 0.33, 0.5, 1 and 3 seconds, with frequencies of 0.75, 0.5, 0.25 and 0.083 cycles per second respectively. For practical clinical purposes, the results with both types of current were comparable.

The data already described for normal muscle were characteristic for all the animals studied (fig. 5).

Within a few days after denervation, the amount of current necessary to excite the muscle by progressive currents of long duration was usually somewhat higher than the amount required by the normal muscle. It began to diminish after about twenty days, and between thirty

Von Kries [20] stated that in curarized muscle of the frog the same strength of current was required to produce stimulation in 0.125 second as was needed for instantaneous stimulation. Lucas found this to be true of the nerve-free pelvic end of the uncurarized sartorius muscle of the toad. However, he attributed the response to the local cathodic contraction, and when he recorded the occurrence of a conducted contraction, he found that the strength of current had to be increased as the time of increase in current became longer.

In our experiments, because of the critical movement in the foot and toes on stimulation and the continued tetanus occurring when at any particular gradient the current was allowed to increase for longer periods, we believe the contraction was a conducted one.
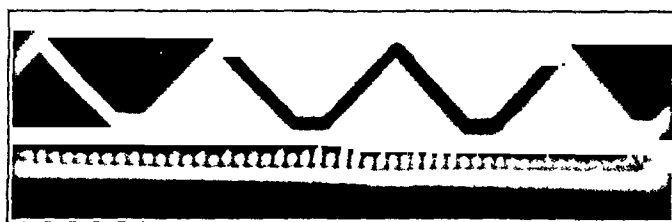
Fig. 6.—Cathode ray oscillogram of the isosceles triangle wave generated by the progressive current apparatus. The interval between the markers represents 0.2 second.
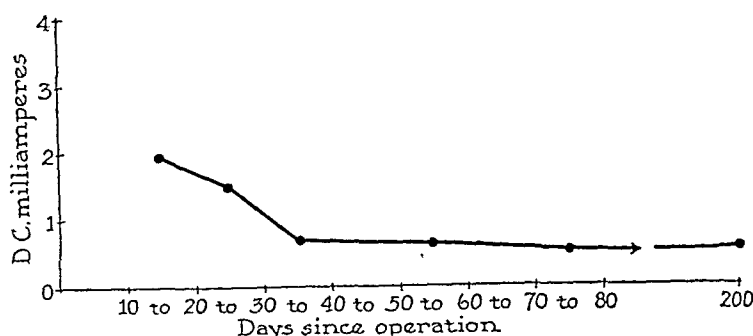
Fig. 7.—Average milliamperage necessary to produce an adequate stimulus with a progressive current of 3.8 seconds' duration in 15 denervated animals at various days after operation.

and forty days it was less than normal and remained so as long as the animals were studied (fig. 7).

In denervated muscles, whether during the period prior to neurotization, in the case of primary sutures, or before suture was done sixty days after section, or after a large portion of the sciatic nerve was removed and injection of absolute alcohol made into the proximal and distal ends to discourage regeneration, there was a response to very small currents whatever the gradient may have been. Thus, it was seen that as long as two hundred and three days after denervation, the rheobasic current being 0.18 milliampere, contraction occurred at 8.8 seconds with 0.27 milliampere (fig. 3).

In contrast to the period of denervation, at times before, and sometimes coincident with, evidence of motor return, the amount of current necessary to produce excitation must be increased considerably above the rheobase when the current is allowed progressively to increase for long periods. Thus, in figure 3, four days prior to the recorded examination made fifty-two days after primary suture the muscle reacted as a denervated one. On the fifty-second day the rheobase was 1.15 milliamperes; at 1.2 seconds contraction occurred with 2.5 milliamperes, at 2.6 seconds with 3.75 milliamperes, at 3.8 seconds with 4 milliamperes and at 8.8

29. von Kries, J., cited by Lucas.[17]

seconds with 5.75 milliamperes. As regeneration progresses, the amount of current necessary for excitation becomes even greater, and a normal pattern is not reached even when fairly good motor recovery has taken place (fig. 8).

In describing the response of muscles possessing a long chronaxia, Lapicque stated in effect that, given a progressive current of a constant rate of increase, diminution of this rate leads to a slight diminution of efficacy of stimulation. This, as has been seen in our experiments, is true only for completely denervated muscles. When, however, neurotization occurs, and for months afterward, and during periods when the chronaxia of the muscle is far longer than that of normal muscle, increasingly large currents are required to excite the muscle when the duration of the progressive current wave becomes

Thus, in a normal muscle a contraction produced at the peak of a progressive current continued to be obtained each time the stimulus was repeated, without any rest, as long as the effect was studied (twenty-five times) at the same amperage. When large continuous currents were passed through the muscle, the passage of a progressive current immediately afterward produced a contraction at its peak, as it did before stimulation with the polarizing current.

In the case of denervated muscle repeated liminal stimulation may be effective at least ten times, whereas in the recovering muscle only the first one or two stimuli are effective. It is true that the liminal amperage is greatest for the recovering muscle, less for the normal muscle and least for the denervated muscle. In the recovering muscle, when the liminal strength
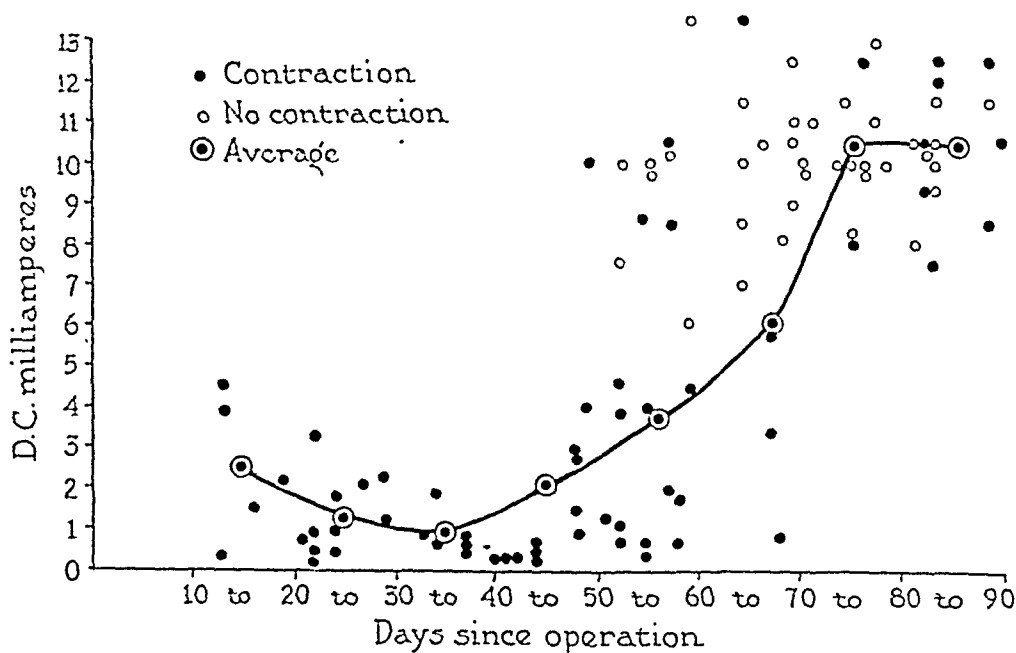
Fig. 8.—Spot graph and average milliamperage necessary to produce an adequate stimulus with a progressive current of 3.8 seconds' duration in 30 animals with primary sutures at various days after operation.

longer and longer or the gradient lower. The response of muscles to progressive currents of long duration is not related in all cases to the chronaxia of the muscle.

We wish to call attention to another difference in the responses of regenerating, denervated and normal muscles to progressive currents. As is well known, when after a galvanic current is passed through a frog's muscle by closure of the circuit with contraction of the muscle, repeated opening and closing of the circuit or long-continued passage of stronger currents results in the closing stimulus becoming ineffective, supposedly because of electrotonus. This "electrotonus" effect may be observed to a conspicuous degree after repeated stimulation with a progressive current in regenerating muscle, to a far less degree in denervated muscle and to a minimal degree in the normal muscle of a cat.

of current necessary to produce contractions at the peak of a progressive current lasting 1.2 seconds was 6.4 milliamperes, repetition of the stimulus was effective only four times.

When at this same amperage and time a denervated muscle was stimulated repeatedly, the stimuli were effective one hundred times, and the same results were obtained for the normal muscle. In the case of the denervated muscle a fatigue-like effect was noticed in that the strength of the contractions diminished with repeated stimuli more than it did in the case of the normal muscle.

SUMMARY

The denervated muscle prior to neurotization may be made to contract by stimulation with an increasing, or progressive, current of very small amperage whatever the current gradient may be.

When neurotization occurs, the current necessary for excitation must be progressively increased the longer the duration of the current or the less steep the gradient.

For normal muscle, at different times, different current gradients must be reached, but no one liminal gradient exists for all times.

CONCLUSIONS

1. The denervated muscle responds to instantaneous galvanic stimuli of very low amperage for at least two hundred and eighty-two days.

2. The denervated muscle responds to a progressive current of long duration at very low amperage irrespective of the current gradient for as long as two hundred and eighty-two days.

3. To excite the neurotized muscle with instantaneous stimuli a much greater current is required.

4. When a successful junction between the regenerating nerve and the muscle has been effected, there is a sudden, pronounced increase in the amperage necessary to produce excitation with progressive currents. The longer the duration of the progressive current, the greater the strength of current necessary to produce excitation.

5. In the normal muscle the minimal current adequate for excitation by progressive currents differs for each long period, or time constant, but there is no liminal current gradient for all durations.

BIOPSIES OF THE BRAIN OF SCHIZOPHRENIC PATIENTS AND EXPERIMENTAL ANIMALS

W. R. KIRSCHBAUM, M.D., AND G. HEILBRUNN, M.D.

MANTENO, ILL.   CHICAGO

Despite the multitude of investigative activities, the question of the histopathology of schizophrenia has remained controversial to date. Perhaps one of the factors contributing to this situation may reside in the well known difficulties associated with the procurement of case material from which valid conclusions can be drawn.

Accessibility to a comparatively large amount of case material, free of complicating factors, such as old age, chronic intercurrent disease, and changes in the brain before, during or after death, would therefore afford one the unique opportunity to contribute to the clarification of the problem. Material selected under such advantageous conditions was found in specimens from the brains of schizophrenic patients obtained for biopsy during prefrontal lobotomy. The patients could be freely chosen for that procedure with regard to age and health. Moreover, the patients were not physically ill at the time the specimens were taken, and a minimum of time elapsed between removal of tissue and fixation.

MATERIAL AND METHOD

Fifteen patients with a condition diagnosed as schizophrenia were selected for bilateral prefrontal lobotomy. Microscopic examination of specimens of the brain of only 12 of the 15 patients will be discussed here, since the results for 3 patients who were over 50 years old may have been related to their age and inclusion of such data might thus yield erroneous conclusions. The changes in the brain of other patients (case 1) appeared to be on an inflammatory, rheumatic basis, and the data were therefore discarded for final evaluation of cerebral changes associated with schizophrenia. The ages of the remaining 11 patients varied from 25 to 50 years, with an average of 35 years; the average duration of the disease for this group was fourteen and seven-tenths years. Throughout examinations, including roentgenographic studies, blood counts and urinalyses, established the presence of perfect physical health, except in the single case just mentioned.

Through burr holes and after crucial incision of the dura, biopsy specimens about the size of a pea were removed from the cortex of the right and of the left prefrontal area before actual leukotomy was performed. Specimens were preserved in 70 per cent alcohol, a 10 per cent concentration of solution of formaldehyde U. S. P., Zenker's fluid and Cajal's bromide–solution of formaldehyde–ammonium solution. Pyroxylin blocks

were used for toluidine blue stains, and frozen sections were prepared with sudan III, Cajal and Penfield stains. Myelin sheath stains, Bielschowsky impregnations and hematoxylin-eosin stains were carried out on paraffin-embedded material. Sections obtained from normal persons who had died suddenly after injury were used as controls.

The lobotomy was performed with the use of pentobarbital sodium and general anesthesia on 1 patient and with ether anesthesia on the remaining patients. Since the ether narcosis could have produced the changes observed, provision of controls was imperative. Such controls were found in the brain of 2 patients who had died during general surgical procedures while under ether narcosis. Furthermore, the specimens of the brain of the patient (case 2) who was operated on while under anesthesia induced by local and intravenous administration of pentobarbital sodium served as an additional control for the possible eventuality of changes due to ether. As a complementary control, biopsies were made of the brains of experimental animals (cats and rats) at various intervals during prolonged ether narcosis, lasting from one to six hours.

Of the 15 patients, 3 died shortly after the operation, a circumstance which provided us with the opportunity of comparing the results of the previous biopsies with those of examination of the whole brain and substantiated the biopsy observations. One of these patients, aged 50, showed conspicious arteriosclerotic changes. His case therefore was included with 4 cases which were held unsuitable for an evaluation pertaining to the scope of this study.

RESULTS

Table 1 indicates the patients' ages at the onset of mental illness and at the time of operation. It lists the most important diseases the patients had undergone and, in a separate column, states whether the patient had previously received shock therapy.

Case 1.—Biopsy of a specimen of the brain of this patient, a woman aged 25 with typical schizophrenia, revealed indubitable organic changes. However, she was observed to have rheumatic heart disease, and a systolic murmur was heard over the apex at the time of the operation. Many ganglion cells were filled with fat droplets. The presence of fat-containing glia cells indicated transport of fat into the adventitial spaces of the smaller vessels of the brain, the walls of which contained considerable deposits of fat in the media and the intima. Toluidine blue preparations showed scattered regions of vacuolar degeneration and shrinkage of the ganglion cells. Isolated areas revealed hypertrophic glia cells and *Gliarasen*.

The patient died five days after lobotomy, of bronchopneumonia. Microscopic examination of the entire brain confirmed the observations at biopsy. The chronic recurrent rheumatic endocarditis and myocarditis were

apparently the cause of the changes noted in the brain. Large areas exhibiting complete loss of neuron cells were visible around small cortical arteries. In the proximity of these areas of paling various forms of degeneration of ganglion cells and increase in fibrous glia cells were evident. Signs of an inflammatory mesodermal reaction were not demonstrable. The case presented a chronic parenchymatous process in the brain, based on vascular disease.

Bruetsch[1] discussed in detail the relation between the changes in the "rheumatic brain" with recurrent endocarditis and the schizophrenic process and emphasized the difficulty associated with identification of the role of the respective processes. In accordance with Bruetsch, therefore, we venture no conclusions with respect to

drocytes. The toluidine blue preparations showed that the ganglion cells were normal in appearance except for some cells which were swollen and contained vacuoles in the cytoplasm. A few fat-containing adventitial cells were seen in engorged vessels.

CASE 3.—A woman aged 38 with a condition diagnosed as schizophrenia died five days after frontal lobotomy. The psychotic behavior of this patient had been characterized by auditory and visual hallucinations, inappropriate laughter, untidiness, impulsiveness and muteness. As in the preceding case, biopsy of specimens of the brain revealed organic changes, manifested by prominent infiltration of fat in the ganglion and glia cells. There were a few fat-laden cells in the adventitia and deposits of fat in the cells of the intima and media of the smaller arteries. In addition, the toluidine blue preparations showed scattered vacuolation and shrinkage of neuron cells, hypertrophy of cytoplasmic glia cells

TABLE 1.—*Clinical Data on Eleven Patients with Schizophrenia Who Underwent Lobotomy*

Case	Sex	Age at Onset of Mental Illness, Yr.	Age at Time of Operation	Past Illnesses	Age of Occurrence	Shock Therapy
2	F	25	37	....	....	Metrazol, 3 yr. prior to operation
4	F	23	35	Scarlet fever; mumps; chickenpox; measles	Childhood	None
5	F	24	28	"Puerperal psychosis"	22	Metrazol, 4 yr. prior to operation
6	F	21	39	Whooping cough; measles; "some infectious diseases"	Childhood 14	None
7	F	21	40	....	....	None
3*	F	26	38	Scarlet fever; measles; influenza	2, 14	Sulfur in oil, 6 yr. prior to operation
8	M	18	50	....	....	None
9	F	21	37	Asphyxiation for 15 min........ Bronchopneumonia	At birth 34	None
10	F	19	33	Measles and influenza..........	Childhood	None
11	F	19	36	Lobar pneumonia with empyema	27	None
12	F	20	26	Diphtheria; scarlet fever; chickenpox; mumps; tonsillitis; mastoiditis	Childhood	Insulin and metrazol 3 yr. prior to operation

* Patient died five days after lobotomy.

the histopathology of dementia praecox from the observations in this case.

CASE 2.—A woman aged 37 was admitted to the institution at the age of 25 with persecutory delusions, visual and auditory hallucinations and periods of excitement. Later she became fearful and mute, and on occasion she attacked other patients. The results of physical examination were essentially noncontributory. In 1937 she was given a series of metrazol treatments, without beneficial results. Lobotomy was performed, with the patient under anesthesia induced by local and intravenous administration of pentobarbital sodium. Biopsy of specimens from the brain revealed fat droplets in the ganglion and glia cells, moderate increase of the cytoplasmic glia cells and no alteration of the oligoden-

and an increased number of astrocytes. Death resulted primarily from a massive hemorrhage into the right frontal lobe and the ventricles. The question whether or not small infiltrations around vessels in the substantia nigra and the neuronophagia in the nuclei around the third ventricle could be attributed to an independent degenerative process or to the preceding lobotomy and hemorrhage in the brain substance remained unanswered.

CASE 4.—A woman aged 35 had the onset of mental illness after her first pregnancy, at the age of 23. The patient expressed many delusions and hallucinations; she stated she felt the influence of machines, roentgen rays, etc., and she had frequent periods of excitement and violence. She screamed frequently. The results of physical examination were essentially without significance.

Toluidine blue stains of pyroxylin-embedded material showed slight changes in the neuron cells of the third layer. A few *Gliarasen* and empty spaces

1. Bruetsch, W. L.: Chronic Rheumatic Brain Disease as Possible Factor in Causation of Some Cases of Dementia Praecox, Am. J. Psychiat. 97:276, 1940.

(*Lückenherde*) were present. The neuron cells contained minute quantities of fat. The cytoplasmic glia cells, while proliferated, were free from fat droplets. A few cells of the arterioles showed infiltration with fat. Slight serous exudation into the perivascular spaces

The toluidine blue stain disclosed pyknosis and shrinking as well as loss of ganglion cells. The dendrites were visible over unduly long distances, the apical dendrites showing corkscrew formation. The cytoplasmic glia cells revealed proliferative changes. Their

Fig. 1 (case 5).—Biopsy specimen of the frontal lobe, showing enlarged glia cells in the third cortical layer, clusters of glia cells and twisted apical dendrites of degenerated neuron cells (toluidine blue stain; pyroxylin-embedded material).
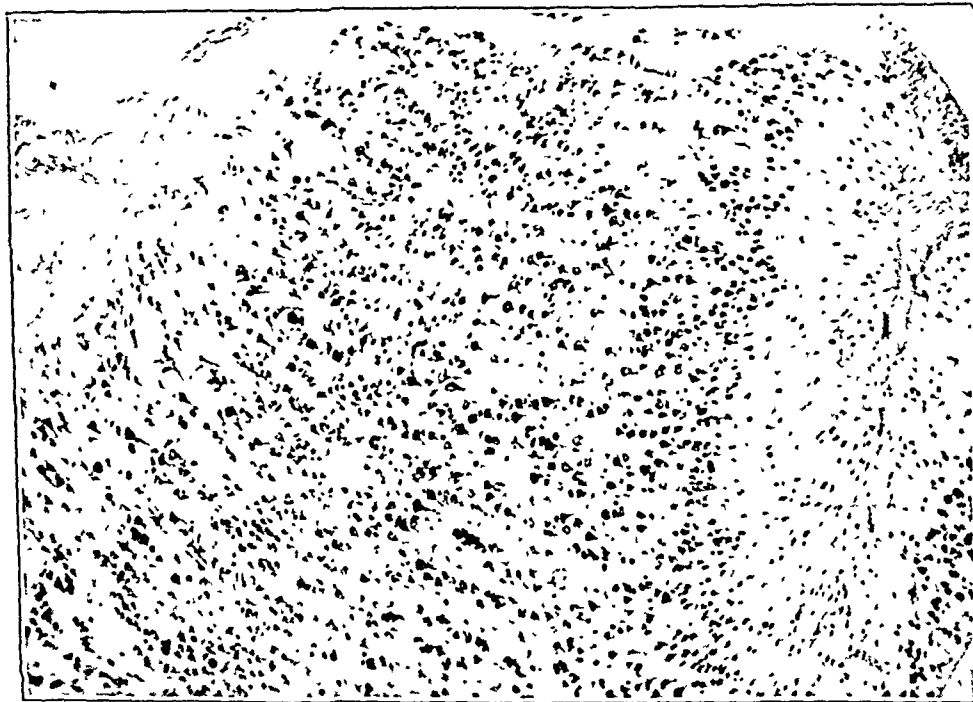
Fig. 2 (case 6).—Portion of a typical biopsy specimen of the frontal lobe, showing slight losses of neuron cells in the third layer, in the upper half of the picture (toluidine blue stain; pyroxylin-embedded material).

was manifest. Myelin sheaths and neurofibrils showed no pathologic change.

Case 5.—A woman aged 28 began to hear voices after childbirth, at the age of 22. She became talkative and unmanageable and struck her baby. For many years she was disturbed, restless and aggressive. There were no pathologic physical signs. Her condition remained unimproved after a course of metrazol injections.

nuclei were enlarged, indented and slightly lobulated. These cells lay isolated or in clusters of four or six (*Gliarasen*). The fibrous astrocytes were increased in number. The oligodendrocytes were slightly swollen. There was infiltration of the neuron cells with minute fat droplets, but none in the small vessels.

Case 6.—A woman aged 39 had the onset of the psychosis at the age of 21. She uttered ideas of

persecution, said she had been poisoned, had periods of excitement, heard the voice of the Lord, laughed in a silly fashion, disregarded her surroundings and became generally withdrawn, but at times was suddenly overactive and violent. There were no physical abnormalities.

The toluidine blue stain revealed among apparently normal neuron cells a few with deeply stained nuclei and cell bodies; some showed vacuolation and swelling, with increased satellitosis; others had disintegrated into mere cell shadows. The cytoplasmic and fibrous astro-
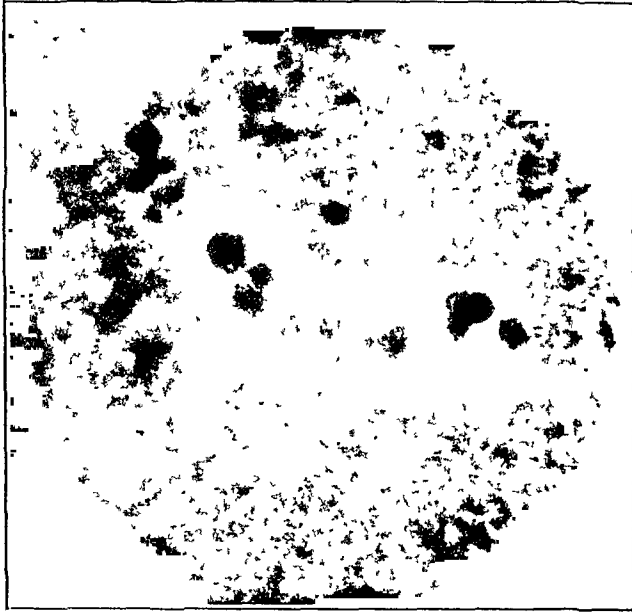
Fig. 3 (case 6).—Fat-laden compound granule cells in the adventitial spaces of arterioles of the brain (sudan III–hematoxylin stain; frozen sections).

cytes were increased in number and size. Some of the nuclei were swollen and slightly indented. Fat droplets were discernible in the ganglion cells, as well as in the astrocytes. The presence of minute fat droplets in cells accompanying the axis-cylinders might indicate disturbance of the myelin sheaths. Myelin stains, however, failed to show any abnormality. The adventitial spaces of several small vessels were filled with fat-laden cells. The intima and the cells of the vessel walls showed infiltration with fat.

CASE 7.—A woman aged 40 had the onset of her mental illness at the age of 21; she worried a great deal, had spells of crying and laughing and talked incessantly. She imagined she heard voices and showed mannerisms. She was occasionally untidy, finally became completely out of contact and at times was suddenly violent. Her physical condition was essentially normal.

The ganglion cells, predominantly those of the third and fifth layers, revealed moderate infiltration with fat. The cytoplasmic astrocytes showed a moderate degree of proliferation. The cells and endothelium of the vessels contained deposits of fat. In the adventitial spaces were a few fat-containing compound granular cells. No toluidine blue stains were made, since all the material had been used for frozen sections.

CASE 8.—A man aged 50 was first admitted to a state hospital at the age of 20. Prior to this admission

he sat around idle for hours, attacked his brother without reason, ran away, took off his clothes and had hallucinations. He had lived in institutions for almost thirty years; he became occasionally excited, shouted the same words and was constantly indifferent. There were no significant physical signs.

Toluidine blue preparations showed mild irregularity in the architectural arrangement of the ganglion cells, many of the cells being vacuolated and clumped and surrounded by numerous glia cells (moderate neuronophagia). The cytoplasmic astrocytes were increased in number and size; the oligodendrocytes were only slightly more numerous. Fat was present in ganglion cells and occasionally in the glia. Slight proliferation of the capillary endothelium was observable. The lymph spaces of the vessel walls harbored a few free fat-laden cells. A few fat droplets in areas of unevenly stained myelin sheaths suggested slight degeneration of these structures. This patient, although the oldest of the 11 patients studied, showed no arteriosclerotic or presenile changes.

CASE 9.—A woman aged 37 had the first psychotic symptoms at the age of 21 years. For the preceding four years she had been in an institution for the feeble-minded. She became disoriented, talked to herself and showed many catatonic features. The results of physical examination were essentially without significance Periods of anxiety and excitement alternated with quiet, manneristic behavior; finally she became completely out of contact. The diagnosis was mental deficiency with psychosis, possibly schizophrenia.

Toluidine blue stains showed some neuron cells with deeply stained cell bodies and processes among the normal ones. Several pyramidal cells appeared shrunken; between them lay cell shadows. The cytoplasmic and fibrous astrocytes showed proliferative activity. Fat droplets were demonstrable in a few neuron cells but rarely in the glia. There was pronounced infiltration of vessel walls with fat, and fat-laden cells were observed in the adventitial spaces. The oligodendrocytic and microglial elements showed no essential changes.

CASE 10.—A woman aged 33 had attempted suicide at the ages of 17 and 18 years because of ideas of persecution; she grimaced, had attacks of excitability and exhibited negativism. She was brought to the institution shrieking that she was being murdered. She paid no attention to her personal appearance and stared into space, under the influence of delusions and hallucinations. During her years in the institution she was destructive and aggressive. The results of physical examination were essentially without significance.

The toluidine blue stain showed many vacuolated ganglion cells and clumped Nissl bodies in the large pyramidal cells. The glia showed slight hypertrophy and pyknosis. Deposits of fat were seen in the ganglion cells and to a conspicuous degree in the vessel walls The endothelial cells were swollen, and some pigment lay around the vessels.

CASE 11.—A woman aged 36 had been psychotic since the age of 19. She read the Bible excessively, neglected her appearance, was under the influence of persecutory delusions, became excited and refused food through fear of being poisoned. She had auditory and visual hallucinations, talked incoherently and at times became aggressive. There were no significant physical signs.

The cortical structure was normal. There were no essential changes in the ganglion cells. The protoplasmic astrocytes showed only moderate increase in number and size; the fibrous astrocytes were slightly more numerous. The oligodendrocytes were unaltered. Stains for fat were not made. Myelin sheath stains revealed no pathologic conditions.

metrazol treatments, without benefit. The stream of thought remained rambling and irrelevant. Emotional response was flat and dissociated. There were momentary flashes of anxiety and aggressiveness.

Cresyl violet stains showed the pia to be slightly thickened. A large number of the ganglion cells were swollen, and a few were shrunken, with the dendrites
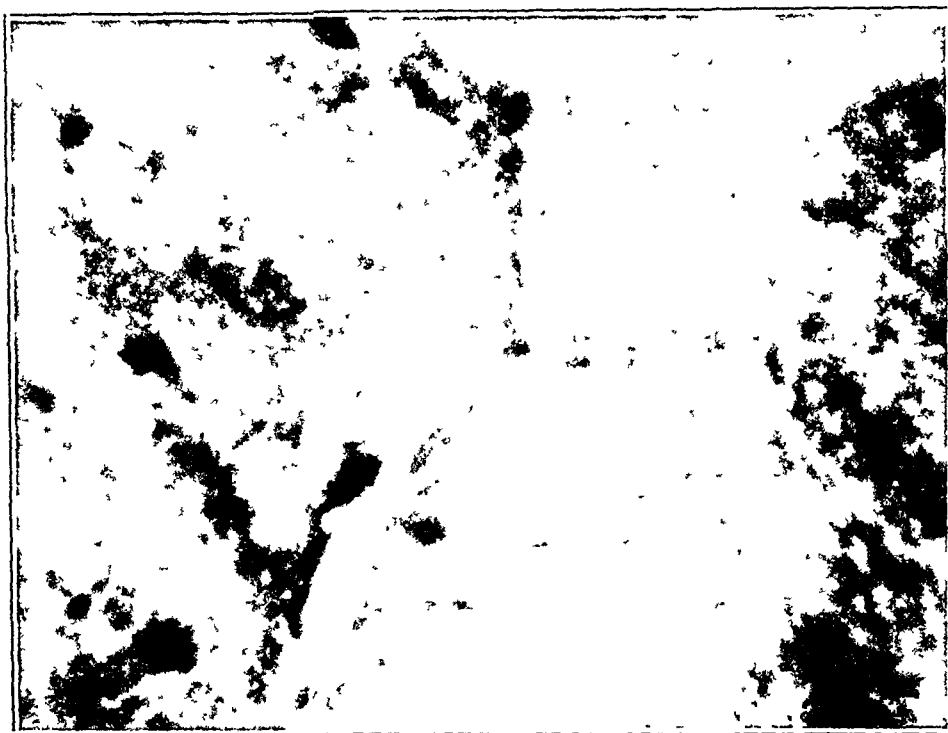
Fig. 4 (case 7).—Lipid deposits in the endothelial cells of arterioles of the brain (sudan III–hematoxylin stain; frozen sections).
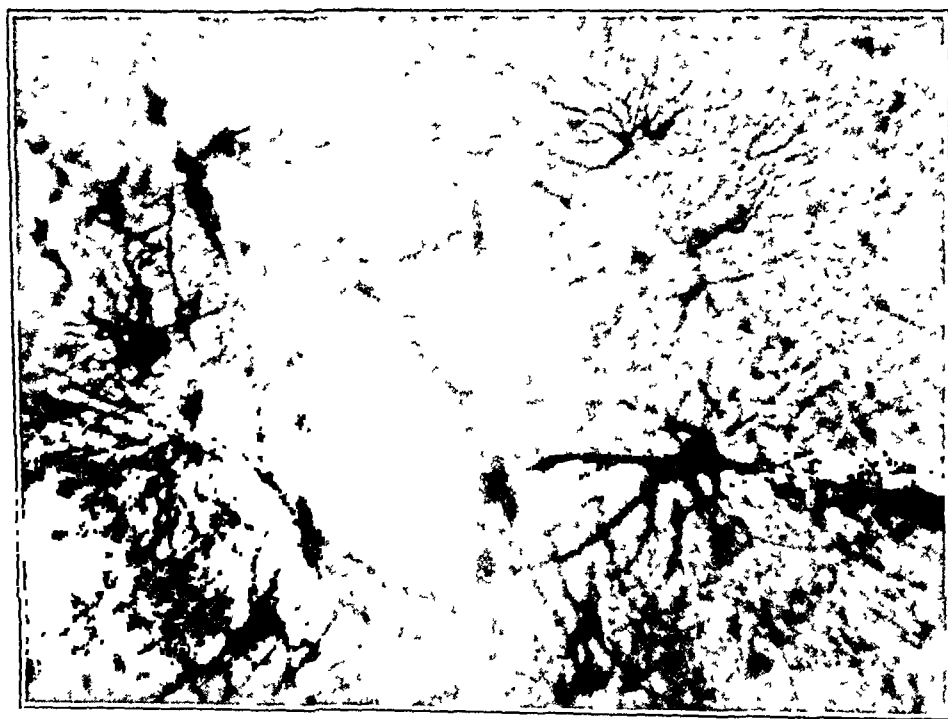
Fig. 5 (case 12).—Increase in size and number of astrocytes, attached to a small artery, in a patient who had received insulin and metrazol shock therapy three years prior to frontal lobotomy (Cajal stain).

CASE 12.—A woman aged 26 had the onset of mental illness at the age of 20; she refused to eat and to see friends and stayed in bed for six weeks. Suddenly she began to cry, demanded a priest, said she saw heaven and heard voices. There were no significant physical signs. She received a full course of insulin and

visible over a considerable distance. Proliferation of the cytoplasmic and the fibrous glia cells became particularly evident in Cajal preparations. Fat was present in both ganglion and glia cells, as well as in some arteriolar cells. The myelin pattern remained unchanged.

The histologic data in the cases are summarized in table 2.

It is difficult to correlate the time factor with the occurrence of the various pathologic changes; neither do the changes in the ganglion cells permit a distinct division into acute and chronic cellular disease. The loss of ganglion cells may be regarded as indicative of permanent change in the cortical architecture, whereas the alterations in the neuron cells noted in the first column of table 2 may possibly be transitory and reversible. A pronounced or extreme production of the astrocytic fibers is likely to be a lasting product of the action of a damaging agent. Similarly, reactions of cytoplasmic glia cells are considered signs of activity of the underlying process. The appearance of fat products and their transportation to

TABLE 2.—*Histologic Data on the Brains of Eleven Patients with Schizophrenia Who Underwent Lobotomy*

| | Ganglion Cells | | Macroglia | | Oligo-dendroglia | Lipid Material in | |
Case No.	Changes	Dropping Out	Cytoplasmic	Fibrous		Glia	Vessels
2	+	—	+	++	—	+	+
3	—+	—	+	+	—	+	++
4	(+)	+	+	..	—	—	(+)
5	—+	—	++	+	(+)	—	—
6	—	—	+	+	—	+	++
7	..	—	+	—	..	+	+
8	—	(+)	++	+	+	+	++
9	+	—	+	+	—	(+)	+
10	—	—	(+)	—	+	—	+
11	—	—	(+)	..	(+)	—	—
12	(+)	—	(+)	++	..	..	(+)

In this table, .. indicates that no examination was made; — means that no changes were discovered; (+) denotes slight alteration, and +, pronounced changes.

the vessels deserve special discussion in connection with the primary influence of ether anesthesia on the brains of human beings and experimental animals.

COMMENT

Biopsies on the brains of schizophrenic patients were performed on a large scale by Elvidge and Reed.[2] Their studies, however, were confined to the white matter, particularly to the oligodendroglia, since their technic of aspirating brain substance from the parieto-occipital region through a needle with a Luer syringe did not provide sufficient cortical tissue.

With Hortega's silver impregnation method these investigators observed swelling and nuclear pyknosis of the oligodendrocytes in schizophrenic, in manic-depressive and in epileptic patients and concluded that the oligodendrocytes of the white matter are "sensitive indicators" of toxic products.

It is unfortunate that our material did not allow examination of the deep medullary layers of the white matter, where Elvidge and Reed almost exclusively noted the pathologic changes, since sufficient white matter was rarely obtained in our specimens. In 2 instances, however, it was possible to see in Hortega stains vacuolation of oligodendrocytes in the white matter.

Of the 11 patients, in only 1 (case 11) were merely negligible changes apparent, whereas in all the others pathologic alterations in the neurons, glia cells or vascular apparatus were disclosed.

The infiltration of fat and the transport of lipid products suggested of course the possibility that the ether narcosis may have been the sole, or a partial, factor responsible for these features, an observation raising the question of their relation to the underlying psychotic process independent of the influence of the ether anesthesia. In several biopsies (cases 3, 6, 7, 8 and 9) isolated cells laden with fat were noted in the adventitial spaces of small arteries and arterioles. Furthermore, fat had infiltrated the cells of the vessel walls and, to a lesser degree, had invaded the nerve parenchyma in the other cases.

From our control material, however, we assume that the ether narcosis could not have been primarily responsible for the presence of fat substances in our biopsy material, for the following reasons: 1. Examinations of the brains of 2 young nonschizophrenic patients who had died during abdominal operations performed with ether narcosis did not show infiltration of fat. 2. Changes in fat distribution were discovered in the brain in case 2, in which operation was done with anesthesia induced by local and intravenous administration of pentobarbital sodium. 3. Mueller[3] demonstrated in animals which were submitted to prolonged and frequently repeated ether narcosis infiltration of fat in ganglion cells and collection of fat both within and around the vessel walls. Weimann[4] reported the occurrence

2. Elvidge, A. R., and Reed, G. E.: Biopsy Studies of Cerebral Pathologic Changes in Schizophrenia and Manic-Depressive Psychosis, Arch. Neurol. & Psychiat. 40:227 (Aug.) 1938.

3. Mueller, B.: Ueber Fettmetamorphose in den inneren parenchymatösen lebenswichtigen Organen nach einfachen und Mischnarkosen, Arch. f. klin. Chir. 75:896, 1904-1905.

4. Weimann, W.: Exogene Intoxicationen, in Bumke, O: Handbuch der Geisteskrankheiten, Berlin, Julius Springer, 1929, vol. 2, p. 58.

of increased fat products in the central nervous system in cases of ether intoxication but, unfortunately, omitted a detailed description. Elvidge and Reed,[2] confronted with the same question of the possible influence of ether on the central nervous system in their 19 cases (the majority of the operations had been performed with ether anesthesia), also made biopsies of brains of animals subjected to ether narcosis. Supported by negative results in these animals, they concluded that the changes they had described in human beings were not attributable to the influence of the ether.

When, in our animal experiments, rats were held under ether narcosis for two hours, biopsies of the brains failed to show any infiltration of fat; in the brains of cats, however, fat droplets appeared in a few cells of the vessel walls after two hours, and the fat-laden elements became more conspicuous with continuation of the ether narcosis. Few free cells were noted in the adventitial lymph spaces, and only occasionally were tiny clusters of isolated fat droplets observed. In all our animals the ganglion and glia cells remained free of lipid substances after a single ether narcosis lasting as long as four to six hours.

In order to determine unreservedly the significance of the presence of these lipid products, one must be aware that they are occasionally observed in the brains of apparently healthy young persons. Therefore, only massive infiltration and transport of fat can be considered pathologic.

The comparative frequency of the fat products seen in the various elements of the nerve tissue of our patients appears essentially to corroborate the observations of Cotton[5] and Josephy.[6] Freeman[7] described large deposits of lipids, both free and collected in phagocytic cells, in the basal ganglia of a 43 year old patient with catatonia who died of suffocation. This author summarized his study thus:

. . . It may be concluded that in the brains of schizophrenic patients intercellular fat is more abundant than in the brains of normal individuals and also appears precociously.

Increase in the number and size of the protoplasmic and fibrous glia cells was rather constant. The especially severe disturbance of the fibrous glia in cases 2, 5 and 12, however, must, in the light of the investigations by Liebert and Weil,[8] be ascribed to the fact that the patients had at one time received metrazol or insulin shock or both forms of therapy.

Evaluation of the changes in the ganglion cells in our material had to be made with the utmost care, in view of the fact that slight swelling and shrinkage of the neurons might be attributed either to the fixation fluid or the staining methods. Spielmeyer warned against overestimation of rarefaction, dropping out of ganglion cells and presence of cell shadows, particularly when the glia appears inactive. On the other hand, numerous careful studies on schizophrenia have revealed notable changes in the neuron cells, comparable to ours, and not explainable on the basis of artefacts. Alzheimer,[9] Ranke[10] and Rosenthal[11] observed diffuse degeneration of ganglion cells, many of them swollen and filled with fat substances and others sclerotic. Cotton[5] demonstrated the frequent occurrence of lipid products in neuron cells. Josephy's[6] studies emphasized vacuolar and lipid degeneration and areas of paling and degeneration of individual neuron cells in distinct layers of the cortical substance, predominantly in the frontal areas. Localization of changes, especially in the frontal lobe, was observed by Goldstein,[12] Zingerle[13] and Hassin.[14] It should be stated that these various authorities expressed the common agreement that the changes bore no specific character but that,

5. Cotton, H.: Fatty Degeneration of the Cerebral Cortex in the Psychoses with Special Reference to Dementia Praecox, J. Exper. Med. 22:492, 1915.

6. Josephy, H.: Beiträge zur Histopathologie der Dementia Praecox, Ztschr. f. d. ges. Neurol. u. Psychiat. 86:391, 1923.

7. Freeman, W.: Lipoid Degeneration Products in the Thalamus and Globus Pallidus in Schizophrenia, A. Research Nerv. & Ment. Dis., Proc. 5:378, 1928.

8. Liebert, E., and Weil, A.: Histopathologic Changes in the Brain Following Experimental Injections of Metrazol, Arch. Neurol. & Psychiat. 42:690 (Oct.) 1939.

9. Alzheimer, A.: Beiträge zur pathologishen Anatomie der Dementia praecox, Psychiat.-Neurol. Wchnschr., 1913, p. 301; Ztschr. f. d. ges. Neurol. u. Psychiat. 7:621, 1913.

10. Ranke, O.: Katatonie mit Hirnschwellung, in Nissl, F.: Beiträge zur Frage nach der Beziehung zwischen klinischen Verlauf und anatomischen Befund bei Nerven- und Geisteskrankheiten, Leipzig, 1913, vol. 1.

11. Rosenthal, S.: Katatonie mit Hirnschwellung, in Nissl, F.: Beiträge zur Frage nach der Beziehung zwischen klinischen Verauf und anatomischen Befund bei Nerven- und Geisteskrankheiten, Leipzig, 1913, vol. 1.

12. Goldstein, K.: Zur pathologischen Anatomie der Dementia Praecox, Monatschr. f. Psychiat. u. Neurol. 25:565, 1909.

13. Zingerle, O.: Zur pathologischen Anatomie der Dementia Praecox, Monatschr. f. Psychiat. u. Neurol. 27:285, 1910.

14. Hassin, G. B.: The Present Status of the Histopathology of Dementia Praecox, Dementia Praecox Stud. 1:7, 1918; Histopathology of the Peripheral and Central Nervous System, ed. 2, New York, Paul B. Hoeber, Inc., 1940.

nevertheless, they must be regarded as the substrate of the psychosis. It appears erroneous to dismiss the observations noted as insignificant—an attitude preferred by Dunlap [15] and Peters. [16]

Schizophrenia is a clinical concept and cannot be considered as a unified disease. It is not at all surprising, therefore, that we found among our "typically schizophrenic" patients at least 2 presenting unequivocal organic disease of the brain (cases 1 and 3), in accordance with the experiences of Ferraro, [17] Malamud and Boyd [18] and others. Ferraro [17] stated the belief that the organic changes in the brains of schizophrenic patients are compatible with the diagnosis of schizophrenia. In certain cases he related the structural damage to functional changes, which he interpreted as complicating, not causative, factors of the psychosis.

The problem remains whether the changes observed are the cause of the psychosis, whether they are a consequence thereof or whether they are mere lateral effects of other factors influencing the central nervous system, without direct relation to the psychosis. Suffice it to say, they resemble changes frequently observed in association with chronic infections and metabolic disturbances. [19]

SUMMARY

Histologic examination of biopsy specimens from the prefrontal cortex of patients with chronic schizophrenia revealed degenerative changes of the ganglion cells and progressive and regressive reactions of the glia and blood vessels, such as are commonly seen in cases of chronic intoxications and metabolic disorders. Study of control material obtained from nonschizophrenic human beings and experimental animals proved that the changes were not attributable to the ether narcosis during which the material had been obtained.

15. Dunlap, C. B.: The Pathology of the Brain in Schizophrenia, A. Research Nerv. & Ment. Dis., Proc. **5**:371, 1928.

16. Peters, G.: Zur Frage der pathologischen Anatomie der Schizophrenie, Ztschr. f. d. ges. Neurol. u. Psychiat. **160**:361, 1937.

17. Ferraro, A.: Recent Views and Leading Points on the Toxic Approach to Mental Disease, Psychiatric Quart. **5**:625, 1931; Significance of Pathological Changes in the Brain of a Case Clinically Diagnosed Dementia Praecox, J. Neuropath. & Exper. Neurol. **2**:84, 1943; **1**:188, 1942; Histopathological Findings in Two Cases Clinically Diagnosed Dementia Praecox, Am. J Psychiat. **13**:883, 1943.

18. Malamud, N., and Boyd, D. A.: Sudden Brain Death in Schizophrenia with Extreme Lesions in Cerebral Cortex, Univ. Hosp. Bull., Ann Arbor **4**:33, 1938

19. Kirschbaum, W. R.: Ueber den Einfluss schwerer Leberschädigungen auf das Zentralnervensystem: I. Gehirnbefunde bei akuter gelber Leberatrophie, Ztschr. f. d. ges. Neurol. u. Psychiat. **77**:536, 1922. Hassin. [14] Ferraro. [17] Weimann. [4]

RELATION OF NARCOLEPSY TO THE EPILEPSIES

A CLINICAL-ELECTROENCEPHALOGRAPHIC STUDY

LIEUTENANT ROBERT COHN (MC), U.S.N.R.

AND

MAJOR BERNARD A. CRUVANT

MEDICAL CORPS, ARMY OF THE UNITED STATES

In Wilson's [1] classic discussion of the narcolepsies strong evidence is produced to justify their inclusion in the family of the epilepsies. Adie [2] earlier postulated, on the basis of his clinical observations, that narcolepsy is a disease entity. In recent years electroencephalography, which has proved to be of much value in the study of the epilepsies, has been focused on the problem of narcolepsy in an attempt to resolve the impasse resulting from these two clinical schools of thought.

Electroencephalographic observations [3] are unanimous as to the occurrence of various stages of "sleep waves" during the sleep component of the narcoleptic seizure. In early sleep, whether physiologic or narcoleptic, the characteristic electroencephalographic pattern is of the low amplitude, high frequency (18 to 25 waves per second) type; as sleep progresses slow wave discharges dominate the record. In deeper sleep 14 per second discharges are recognized as a transient phenomenon.[4] Blake and her associates [3c] have expressed the opinion that the chief distinguishing feature between normal and narcoleptic sleep is the precipitous onset of the latter. Dynes and Finley,[3a] on the basis of a series of 22 cases, arrived at the conclusion that the "spontaneous" interseizure electroencephalograms of morbid sleepers (narcoleptic patients) show no characteristic similarities to the wave patterns associated with the epilepsies.

In the present communication a detailed clinical and electroencephalographic study of 10 cases of a severe disturbance of sleep function is presented. The disorder manifested itself in paroxysmal, diurnal, entirely inappropriate and uncontrollable sleep. In 5 cases affective stimuli induced cataplectic muscular phenomena. In this series of cases inconstant, but definite, abnormalities of the electroencephalogram were observed in the waking state. Moreover, these abnormalities were qualitatively similar to, but quantitatively less prominent than, the electroencephalographic changes commonly associated with the epilepsies.

REPORT OF CASES

CASE 1.—*History.*—B. J. S., a Negro aged 23, had had a formal fifth grade education, but his acquired learning was far above this level. He was unable to carry out his duties as a soldier on account of irresistible attacks of sleep.

Mild seizures of sleep first occurred in 1927, at the age of 8 years. At the age of 9 years he sustained a fracture in the left parietal region of the skull. At this time the intensity of the narcoleptic spells became accentuated. Attacks of sleep occurred from three to five times a day. For the last fourteen years there had been no increase in frequency or intensity of the attacks. The patient stated that sleep was ushered in by "a sort of curtain coming over" his eyes. He said that after the sleep state he felt weak for several minutes. Numerous automobile accidents had occurred as a result of his inability to keep awake, even while driving. Nocturnal sleep was not impaired. There was no evidence of cataplectic phenomena.

He stated that he had had only the ordinary diseases of childhood. He denied having had any serious illness other than the attacks of sleepiness. He said that 1 sister, at the age of 14 years, began to have narcoleptic attacks of even greater severity than his own. One brother was said to have had "spasms," which later disappeared. Ten other siblings were all presumably normal. A maternal aunt had narcoleptic seizures beginning at the age of 20 years. She "slept almost all the time." She died at the age of 40, while "asleep."

Examination.—The patient was well developed and lightly pigmented. He stuttered somewhat during ordinary conversation. Occasionally he showed an involuntary, mild, coarse tremor of the body. The muscles

1. Wilson, S. A. K.: The Narcolepsies, Brain **51**: 63-109, 1928.

2. Adie, W. J.: Idiopathic Narcolepsy: A Disease Sui Generis, with Remarks on the Mechanism of Sleep, Brain **49**:257-306, 1926.

3. (*a*) Dynes, J. B., and Finley, K. H.: The Electroencephalograph as an Aid in the Study of Narcolepsy, Arch. Neurol. & Psychiat. **46**:598-612 (Oct.) 1941. (*b*) Gibbs, F. A.; Davis, H., and Lennox, W. G.: The Electroencephalogram in Epilepsy and in Conditions of Impaired Consciousness, ibid. **34**:1133-1148 (Dec.) 1935. (*c*) Blake, H.; Gerard, R. W., and Kleitman, N.: Factors Influencing Brain Potentials During Sleep, J. Neurophysiol. **2**:48-60, 1939.

4. Davis, H.; Davis, P. A.; Loomis, A. L.; Harvey, E. N., and Hobart, G. A.: Human Brain Potentials During the Onset of Sleep, J. Neurophysiol. **1**:24-38, 1938.

of the iris contracted slowly to light and in convergence. General perception of sensory stimuli and motor function seemed unimpaired. No pathologic reflex pattern was elicited. Ophthalmoscopic study showed moderate entwining of the retinal arteries and veins, most pronounced on the left side. The basal metabolic rate measured — 23 per cent on Feb. 12, 1942 and — 40 per cent on February 16. The Wassermann reaction of the blood was negative.

Electroencephalographic Studies.—Repeated electroencephalographic studies showed dominant alpha sequences,

A

I 20 μV

B

C
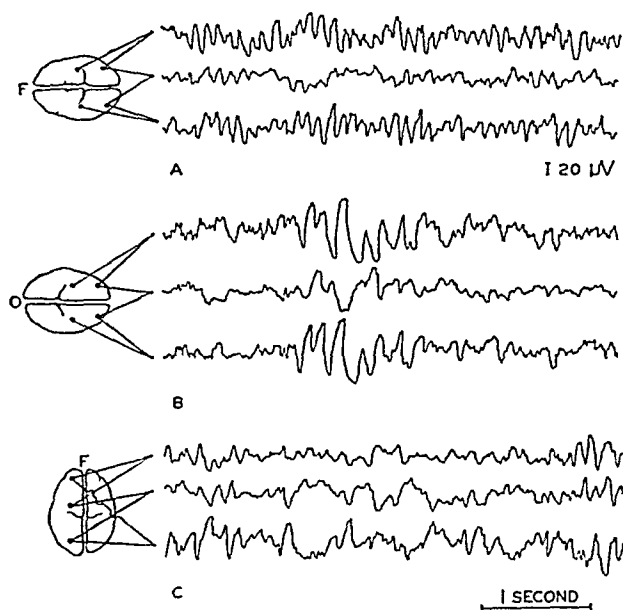
I SECOND

Fig. 1 (case 1).—*A*, basic pattern when the patient was awake; *B*, burst of low frequency activity, unassociated with sleep or movement; *C*, waves appearing during early sleep.

the frequencies ranging from 8.5 to 10 per second (fig. 1 *A*). Short bursts of waves of lower frequency (approximately 6 per second) were observed in the frontal leads. These volleys were unassociated with any recognizable motor activity or evidence of sleep (fig. 1 *B*). During the recording, for approximately a two minute interval, breathing became audible, and volitional response to auditory stimuli was no longer elicited. The electroencephalogram (fig. 1 *C*) associated with this "sleep" state appeared similar to that obtained in early normal sleep. Hyperventilation for two minutes resulted in a moderate increase in the low frequency component of the basic "awake" type of electroencephalogram.

CASE 2.—*History.*—C. McL., a white man aged 25, reported at "sick call" when he became worried lest he fall asleep on guard duty and be court-martialed.

As well as he was able to ascertain, he had had spells of sleepiness ever since he was born. The attacks were not preceded by an aura. The seizures occurred two to six times a day. He had been arrested for speeding and passing red traffic lights during these spells. On awakening from an attack he felt well and was able to resume whatever task he was performing at the time. There had been little variation in the pattern, intensity or frequency of the seizures. They were uninfluenced by any medication. Any strong excitement made him "weak in the knees." Nocturnal sleep was undisturbed except for occasional "nightmares."

He stated that at the age of 2 years he had "milk poisoning" and nearly died. This illness left him "ner-

vous" and with a tendency to stutter. This disturbance was more noticeable during periods of tension. In addition to the ordinary diseases of childhood and an attack of diphtheria, he had influenza in 1935.

The patient was an only child. There was no history of narcolepsy in the family. The mother was an invalid; she had had one or two "nervous breakdowns" and had been operated on for the relief of hyperthyroidism. Two maternal aunts also suffered from hyperthyroidism.

Examination. — The patient was short, moderately stout and blond. He appeared serious and intelligent. Aside from stuttering, paralysis of the right pharyngo-palatine muscle and brisk, but equal, deep tendon reflexes on the two sides, no important abnormalities at the gross neurologic level were elicited. The temperature ranged around 97.5 F., and the pulse rate averaged 65 beats per minute. Several determinations of the basal metabolic rate showed only moderate decrease in the utilization of oxygen. The cholesterol content of the blood was 0.182 mg. per hundred cubic centimeters and the dextrose tolerance curve showed only a slight central elevation.

Electroencephalographic Study.—The electroencephalograms were characterized by a dominant alpha pattern. The voltage was relatively high, but well modulated. There was a well regulated frequency of approximately 10 waves per second (fig. 2 *A*). Occasional bursts of 6 per second waves arose in the midst of prominent alpha activity (fig. 2 *C*). Narcoleptic spells during the recordings were associated with waves of the type usually seen during physiologic sleep. Auditory stimuli (impact of metal rods) during the narcoleptic seizures brought out excellent volleys of alpha waves (fig. 2 *B*). Hyperventilation induced no gross change in the electroencephalogram.

A

I 20 μV

B

NOISE

I SECOND

C
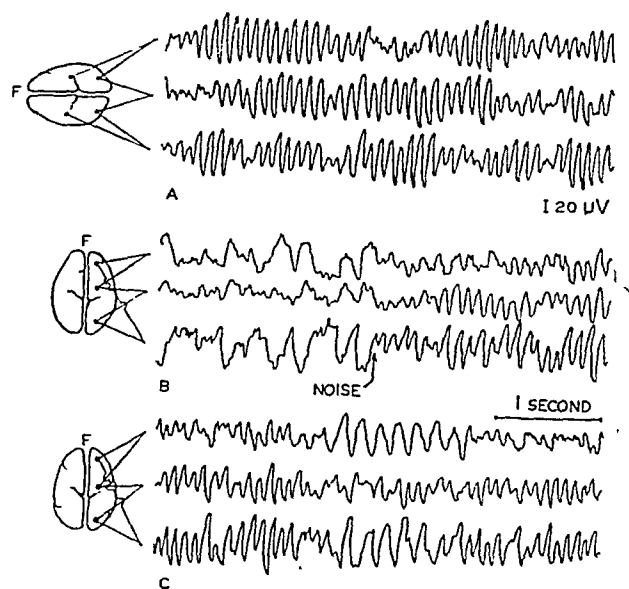
Fig. 2 (case 2).—*A*, basic pattern; *B*, pattern during sleep of medium depth, with appearance of alpha activity following noise; *C*, volley of 6 per second waves.

CASE 3.—*History.*—C. R., a Negro aged 21, a graduate of a Pittsburgh high school, had intense, uncontrollable states of sleepiness. He dropped behind on marches, slept at meals and at lectures and fell asleep whenever he was left alone.

Attacks, which were first noted at the age of 3 or 4 years, were preceded by a mild headache. The cephalalgia became more intense if he could not sleep.

A typical instance of the patient's general behavior may be obtained from his boxing activity. While waiting to box, he would fall asleep; then he would "whale the devil" out of his opponent and five minutes later was again asleep. Nocturnal sleep was not disturbed. Emotional excitement made him "weak all over" and produced "a heavy feeling in the stomach."

He was struck in the left eye with a baseball bat in 1938; since then he had had ptosis of the left eyelid. He stated that drooping of the lid was more obvious when he was tired or at the end of the day. He had
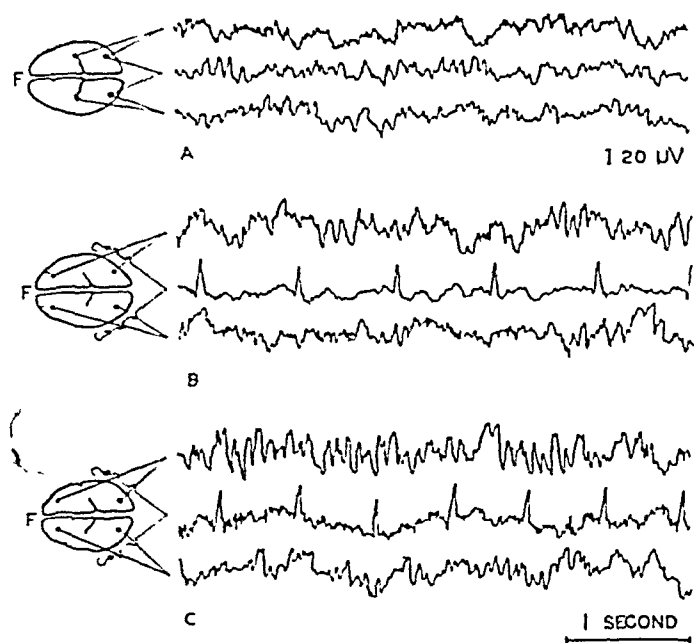
Fig. 3 (case 3).—*A*, basic pattern; *B*, pattern before hyperventilation; *C*, pattern after one and a half minutes of hyperventilation.

had the ordinary diseases of childhood. He denied having had influenza or grip.

He stated that 1 sister had an abnormal tendency to sleep but that her attacks were not as severe as his own. His mother had spells of dizziness, "from high blood pressure," but she did not "fall out."

Examination.—The patient was rather tall and thin and appeared intelligent. He talked well and appropriately. There was pronounced ptosis of the left eyelid. Enopthalmos was not observed. The pupils were round and equal and measured about 2.5 mm. in diameter. The muscles of the iris reacted well to light and in accommodation. On lateral gaze nystagmoid jerks were observed. No evidence of dysfunction of the perception of sensory stimuli was elicited. Deep tendon reflexes were active and equal on the two sides. No gross motor dysfunction was recognized.

Electroencephalographic Study.—The electroencephalograms showed a random, high frequency discharge of low amplitude (fig. 3 *A* and *B*). Occasional oscillations of long duration were observed; these had distorted, square wave characteristics (not shown in the figure). No narcoleptic seizures were manifest during the tests. Hyperventilation evoked sequences of rhythmic oscillations approximately thirty seconds after the onset of overbreathing. This rhythmicity became strongly dominant after about two minutes of hyperventilation (fig. 3 C). The R spike of the electrocardiogram was a prominent characteristic of the records from the biaural leads.

CASE 4.—*History.*—C. L. M., a Negro aged 22, began school at the age of 8 years; by the age of 17 years he had progressed to the fourth grade. He was relieved

of army field duty because of his inability to stay awake and was then assigned to duty as a furnace fireman. Here he had to be constantly watched for fear that he would sleep on the furnaces and injure himself.

From his statements it was apparent that he had suffered from a sleep disorder all his life. He estimated that he slept eighteen hours a day. He stated that the onset of sleep was not accompanied by any aura. The intensity of the narcoleptic disturbance remained practically constant. He was said often to show violent outbursts of temper when he was awakened. When he became emotionally excited, he fell to the floor but did not lose consciousness.

He had whooping cough at the age of 7 years and measles at the age of 14 years, at which age he struck his head while swimming and was knocked unconscious. Since then he had had headaches most of the time. At the age of 18 he had an attack of pneumonia. He denied having had influenza or grip.

He stated that all his brothers were hot tempered. One brother (aged 14 years) spent most of his time in bed sleeping; essentially he got up only to eat. A younger sister had "convulsions."

Examination.—One was immediately attracted by the continuous, shy, faint smile on the patient's face. He was tall and not darkly pigmented. In view of the subject's limited education and general sleepiness, his conversation was good. His answers to queries were often delayed (he said he was hard of hearing), but they were always appropriate. Jerking of the head and body was observed, the movements being random and of small amplitude. The nuchal flexure was almost absent. The face showed some static asymmetry. The left side of the face was flattened. Dynamic (volitional and
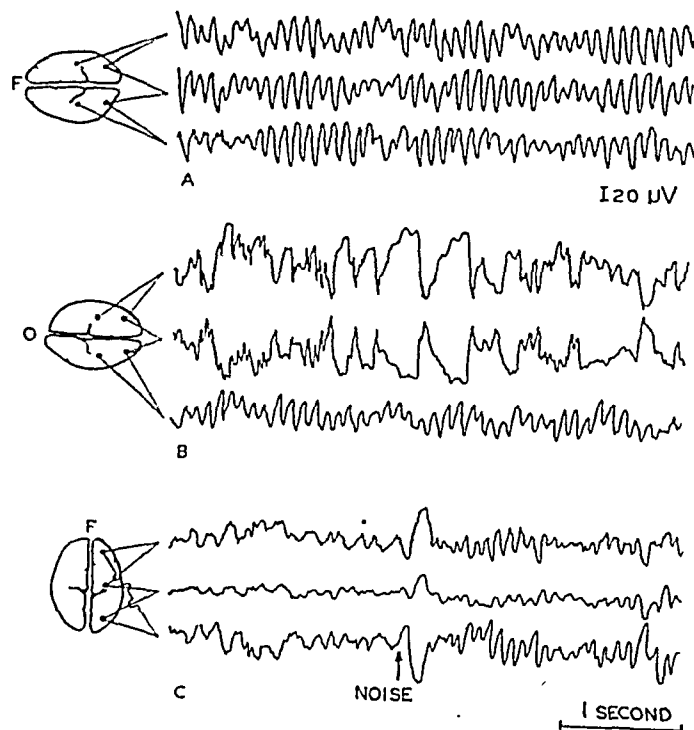
Fig. 4 (case 4).—*A*, basic pattern; *B*, abnormal wave forms in the left frontal lead; *C*, waves appearing during sleep, with response to an auditory stimulus.

emotional) motor function of the facial muscles appeared intact. The patient was able to hear a watch tick at a distance of over 30 cm. with the right ear and at a distance of only 5 cm. with the left ear. In each ear bone conduction was more acute than air conduction. There was moderate reduction in volume of the muscles of the left upper extremity. The biceps region had a circumference of 22.5 cm. on the right side and of 21 cm. on the left side. The hand grip was equally dimin-

ished on the two sides. The finger to nose test, with the eyelids closed, showed some decomposition of movement and inaccuracy of placement on both sides. Sensory perception to pinprick, light touch and vibration did not appear grossly disturbed. Stereognostic function seemed intact. Deep tendon reflexes were active and approximately equal on the two sides. No pathologic reflexes were elicited. Clonic phenomena were not observed. Stereoscopic roentgenograms of the head showed no gross abnormality. The Kahn reaction of the blood was negative.
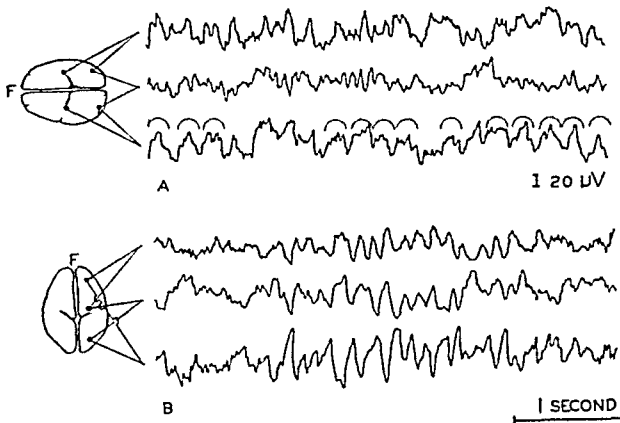
Fig. 5 (case 5).—*A*, basic pattern, with predominantly low frequency discharges; *B*, burst of slow waves.

Electroencephalographic Examination.—There was a dominant alpha frequency of approximately 10 waves per second (fig. 4 *A*). A transient abnormality, consisting of asymmetrically peaked waves of large amplitude and variable frequency (fig. 4 *B*), was observed in the left frontal lead. Narcoleptic seizures were evident in each recording. In one tracing (fig. 4 *C*) wave forms characteristic of the early stages of sleep were clearly evident, together with the influence of auditory stimuli. The "on" effect of the stimulus was pronounced. Hyperventilation failed to induce any notable change in the electroencephalogram.

CASE 5.—*History.*—R. L. R., a Negro aged 19, whose formal education was limited to the tenth grade, was greatly hampered in his service activity by irresistible attacks of sleep.

His mother stated that these spells began during childhood. The attacks were more numerous during fatigue states, but under any condition he had several seizures a day. No history of aura was elicited; he "just got sleepy." As a boy he would go to a "movie" about 10 a. m. and often leave after 4 p. m., but still could not recall the picture in a connected way. Nocturnal sleep was in no way disturbed. Excitement did not induce evidence of cataplexy.

He had had the ordinary diseases of childhood, including diphtheria. In 1941 he was treated for gonorrhea and a lesion of the penis, which he stated was not due to syphilis. At times he drank alcohol to excess. He denied having had influenza or grip.

His mother was apparently addicted to the use of alcohol. The father was said to be a "constitutional psychopath." It was stated that a maternal first cousin, aged 44, was narcoleptic and that a maternal aunt had been institutionalized for a mental disorder.

Examination.—The patient was tall, heavy and darkly pigmented. He talked well and appropriately. He readily comprehended and responded well to fairly complex questions. The pupils were round and equal and

measured about 1.5 mm. in diameter. The muscles of the iris reacted to light and in accommodation. There was ptosis of the right eyelid. With increased intensity of illumination in the left eye the ptotic lid closed reflexly. Sensory and motor function showed no gross general or local impairment except that already noted. Deep tendon reflexes were active and equal on the two sides. Abadie's sign was present bilaterally.

Electroencephalographic Study.—Figure 5 *A* shows the pattern characteristic of the waking state obtained from bipolar parieto-occipital leads. The main deflections have durations close to two hundred milliseconds (5 waves per second). Superimposed is faster activity, which tends to obscure the fundamental frequency. There are occasional shifts of dominance of the slow discharges from the right to the left cerebral hemisphere. For a relatively short interval during the recording many sequences of fast (20 to 22 waves per second) and slow (6 waves per second) activity were observed (fig. 5 *B*). The subject was not asleep at this time. Hyperventilation brought out no marked change in the electroencephalogram.

CASE 6.—*History.*—O. M., a Negro aged 35, appeared dull and sleepy. The limit of his formal education was the third grade of grammar school. He reported his narcoleptic disorder almost immediately after joining the army, when he became apprehensive that it might get him into serious difficulties.

Attacks of sleep were first noted about 1930. He stated that about 1925 he had an attack of "influenza pneumonia." He had a high fever and was in bed almost a month. At the time of examination he had two to six narcoleptic attacks daily, each lasting about
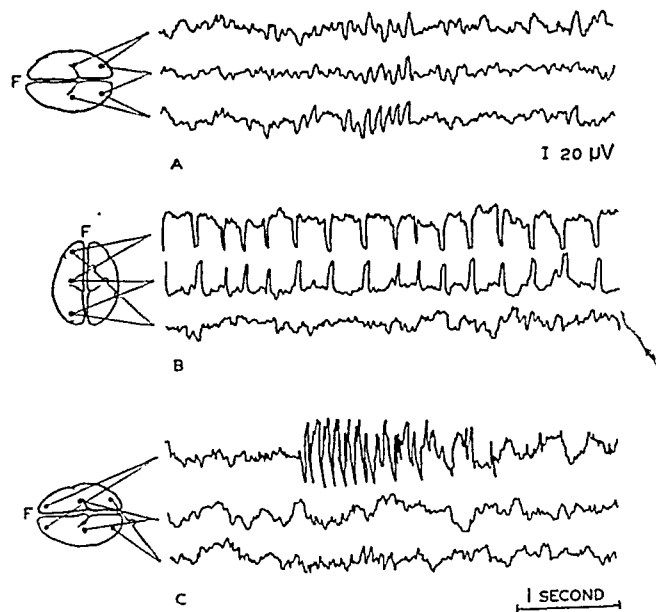
Fig. 6 (case 6).—*A*, basic pattern; *B*, psychomotor discharge in the left parietal lead; *C*, abnormal wave forms in a later record.

five minutes. He would fall asleep under almost any circumstance—at drill, at meals or at the movies. Each spell came on with an overpowering desire to sleep that he could not fight off. He denied having any cataplectic episodes during excitement. He often walked in his sleep.

The early medical history was vague, but one gathered that he had had most of the diseases common to childhood. Aside from the "influenza pneumonia" and

accidental trauma to the left leg, he appeared to have been in good health.

The family history was noncontributory; actually, he was vague and uncommunicative with respect to it. He stated he had a child 12 years old, who was well.

Examination.—The patient was tall, thin and darkly pigmented. No pronounced deviation from the normal was evident. He talked slowly but well. No abnormal sweating or greasiness of the skin was observed. There was no increase in salivation. The pupils were approximately 3 mm. in diameter and were equal. The muscles

A   I 20 µV

B

C   I SECOND
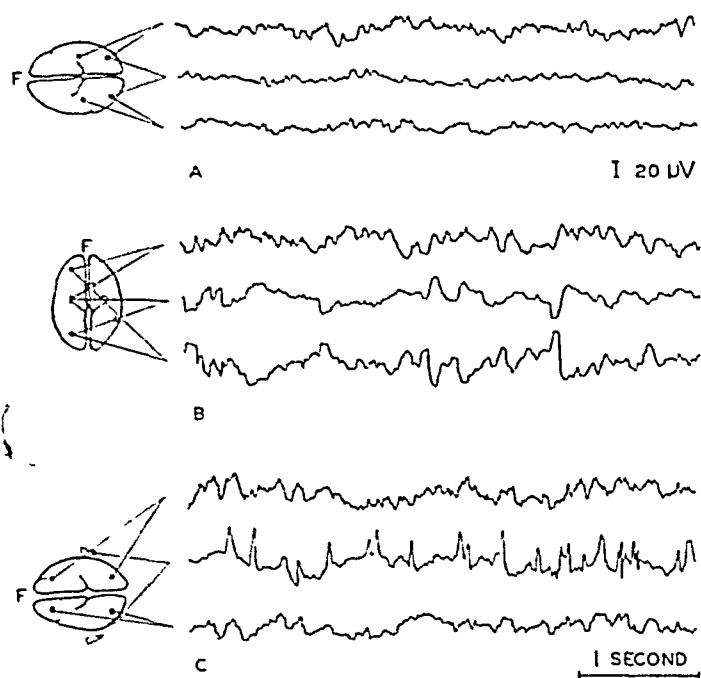
Fig. 7 (case 7).—*A*, basic pattern; *B*, waves appearing during sleep in a narcoleptic seizure; *C*, spike waves in the lead from the left ear.

of the iris reacted well to light and in convergence. Motor function appeared normal. Perception of sensory stimuli was diminished over the lateral aspect of the left leg. This extremity had been the site of spike and bullet wounds. Deep tendon reflexes were decreased in amplitude but were active and equal on the two sides. A dextrose tolerance test gave an entirely normal curve. The Kahn reaction of the blood was negative.

Electroencephalographic Study.—No narcoleptic spells were recognized in the electroencephalograms. Basically, the tracing revealed waves of low amplitude. The occipital leads showed only a moderate proportion of 10 per second waves (fig. 6 *A*). In figure 6 *B* is shown a burst of abnormal wave forms from the left parietal lead, which persisted for nearly three minutes. In figure 6 *C* the abnormality appears in the frontal region in a record taken two days after the tracing in figure 6 *B*. This abnormality consists of a volley of high voltage waves of one hundred milliseconds' duration, followed by oscillations with fundamental durations two to three times as long.

CASE 7.—*History.*—W. L. W., a Negro aged 27, had progressed in his formal education in an entirely normal manner to the second year of high school. He tried to conceal his uncontrollable tendency to sleep, but it was noted that whenever the order was given to stand "at ease" he fell asleep. This defect led to his hospitalization.

He stated that in 1928 he had an attack of "grip" and that since then he had had an ever progressive tendency to sleep. However, his mother stated that he had suffered from seizures of sleeping since childhood. She also said that before his attacks of sleep he "shook

and worked his mouth." Nevertheless, during the past four or five years he had shown an almost cyclic recurrence of diurnal irresistible sleep states. He had on several occasions awakened to find that he had crossed busy city streets. This made him feel "shaky." His friends stated that during these states of sleep walking his eyelids were shut but he could carry on conversation. At night he often awakened from deep sleep and remained awake for one or two hours. Strong emotion made him "weak all over."

He had had the common diseases of childhood, but he did not have mumps until the age of 15 years. When he was 13 years old he had the aforementioned attack of "grip," and at the age of 16 he had rheumatism, which immobilized him for approximately one month.

Two siblings appeared entirely normal. Another brother, aged 21, had attacks of sleep like the patient's.

Examination.—The patient was of medium size, well developed and darkly pigmented. He talked slowly but well and appropriately. He walked with a slow but not abnormal gait. The head was round; the facial features were blunt. The pupils were round and equal and measured approximately 2 mm. in diameter. The muscles of the iris reacted well to light and in convergence. The cranial nerves appeared free from gross abnormality. No motor or sensory dysfunction was observed. The deep tendon and superficial reflexes were active and equal on the two sides. Abadie's sign was noted bilaterally, but Biernacki's sign was not present. Determination of the basal metabolic rate, the dextrose tolerance test and serologic examinations of the blood all gave normal results. Stereoscopic roentgenograms of the head revealed nothing abnormal.

Electroencephalographic Study.—The electroencephalogram was of the low amplitude, random frequency type. Occasional rhythmic sequences of about 17 waves

A   I 20 µV

B
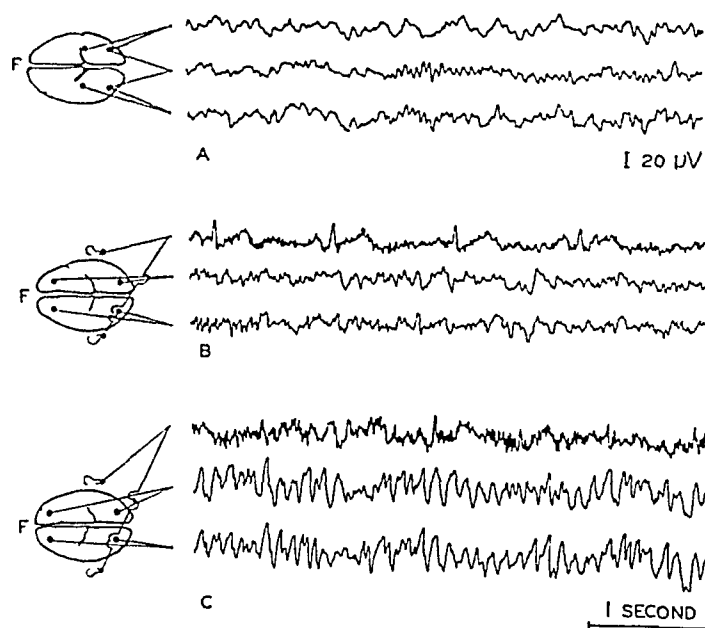
C   I SECOND

Fig. 8 (case 8).—*A*, basic pattern; *B*, pattern before hyperventilation; *C*, pattern during hyperventilation, with rhythmic fronto-occipital activity.

per second were observed (fig. 7 *A*). During the narcoleptic state wave forms characteristic of normal sleep were recognized (fig. 7 *B*). The left ear lead (middle line of figure 7 *C*) showed random spike forms, which were in no way synchronous with the radial pulse.

CASE 8. — *History.* — C. T., a white man aged 25, was referred for electroencephalographic study by Dr. Antoine Schneider, Washington, D. C. The patient appeared intelligent. He said his life had been ruined

by "narcolepsy." At the age of 12 years he had "spinal meningitis," and for several months after the infection he was "cross eyed." In his fourth year of high school, at the age of 17, he began to have spells of sleepiness. These states had become progressively more intense, so that now he often awakened to find that he had traversed several busy streets. He greatly feared that this might result in a serious accident. However,
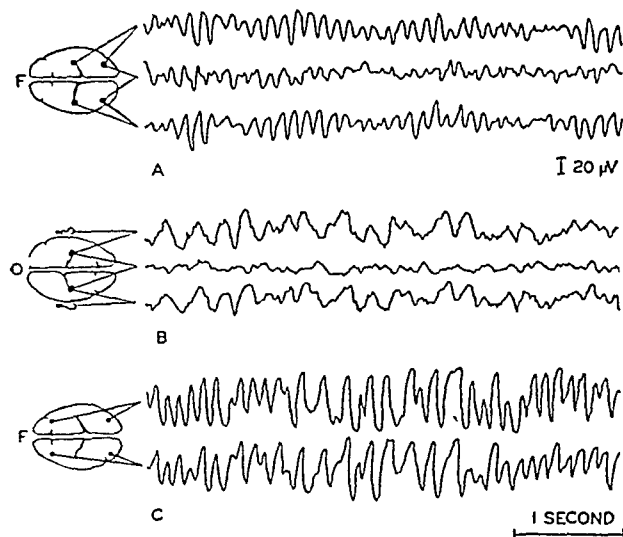
Fig. 9 (case 9).—*A*, basic pattern; *B*, during narcoleptic seizure; *C*, volley of slow waves during hyperventilation.

he was most depressed by his attacks of sleep while he was working. This condition had made it difficult for him to keep a position for any length of time.

Examination.—The patient was of medium size and appeared well nourished and free from gross neurologic abnormalities. The head was large, but not abnormally so. Ophthalmoscopic examination showed some retinal hypervascularity; the artery-vein ratio was approximately 1 : 1. No gross changes in the disk or retina were observed.

Electroencephalographic Study. — Only one electroencephalogram was taken. The pattern was that of a low amplitude, random frequency. Oscillations of low frequency were prominent in the symmetric parietooccipital records. The transverse occipital derivations showed dominant sequences of activity of approximately 20 waves per second (fig. 8 *A*). *B* and *C* of figure 8 show the effect of hyperventilation. The control, *B*, has little or no evidence of alpha activity. During hyperventilation many rhythmic 9 per second waves were observed. This definite alpha pattern made its appearance within ten seconds after the onset of overbreathing. A maximum was soon reached and was roughly maintained during the entire period of hyperventilation (three minutes). Within a minute after the cessation of overbreathing the 9 per second waves were replaced by oscillations approximating the control type.

CASE 9.—*History.*—H. G., a Negro aged 18, born in Alabama, had completed the eighth grade of grammar school. He could not keep from sleeping; on the march he stumbled, and in the "at ease" position he immediately went to sleep. He stated that between the ages of 8 and 10 years he began to sleep at inappropriate times. At about the age of 15 these attacks of irresistible sleep occurred four to five times a day. From that time their intensity and frequency remained constant. Aside from an intense desire to sleep no aura was

experienced. He denied any dystonic reaction to emotional stimuli. Nocturnal sleep was often interrupted by long intervals of insomnia.

He had had the common diseases of childhood, with no apparent sequelae. At the age of 16 years he had influenza.

He had 5 sisters and 1 brother, all of whom were said to be well. His father, a veteran of World War I, had left hemiplegia in early middle life. The nature of the disorder was not determined.

Examination.—The patient was well developed, well nourished and darkly pigmented. He had a singularly intelligent face. During conversation, particularly when he became animated, he manifested a hesitancy of speech that was closely akin to stuttering. No gross impairment of motor or sensory function was observed. All reflexes were active and equal on the two sides. No pathologic reflexes were elicited.

Electroencephalographic Study.—The electroencephalogram showed a beautiful alpha pattern (10 waves per second) in the occipital region (fig. 9 *A*). Narcoleptic seizures were observed during the recording (fig. 9 *B*). The wave forms were characteristic of the pattern seen during sleep of medium depth. During hyperventilation volleys of slow waves (approximately 6 per second) were recognized (fig. 9 *C*).

CASE 10.—*History.*—J. H. S., a Negro aged 35, a native of Pittsburgh, had received only a seventh grade education. His general conversation was mature in context and vocabulary. Because of his inability to remain awake it was impossible for him to carry out his military duties.

In September 1932 the patient weighed 165 pounds (74.8 Kg.); within three months he weighed 230 pounds
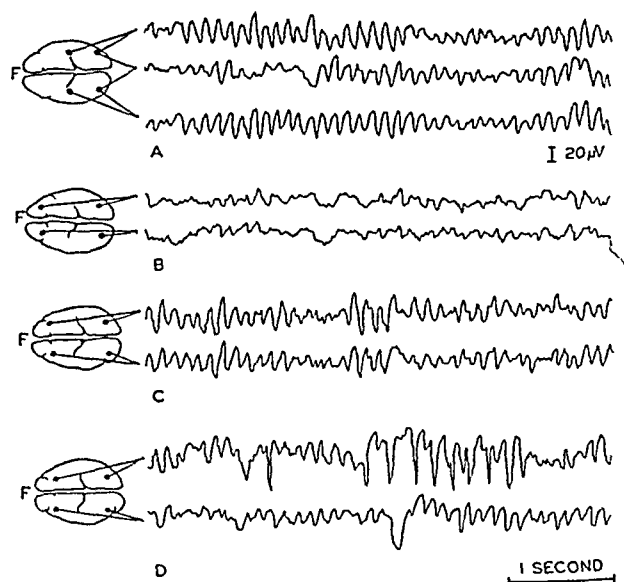
Fig. 10 (case 10).—*A*, basic pattern; *B*, waves appearing during early sleep, just before hyperventilation; *C*, pattern at the beginning of hyperventilation; *D*, abnormal waves during early hyperventilation.

(104.3 Kg.). During the interval of increasing weight he began to have dizzy spells, which continued up to the present. During such spells he stuttered and found it difficult to "think and say things." He did not lose consciousness at this time but became "weak all over." These attacks occurred two or three times a day.

After each seizure he slept. At times, however, sleep became irresistible, even without the prelude just described.

Aside from the ordinary diseases of childhood, he had influenza in 1923 and again in 1929.

He denied that any other member of his family had any nervous disturbance or sleep disorder. His family consisted only of average-sized persons.

Examination.—The patient was lightly pigmented, tall and obese. There was no definitely abnormal distribution of fat. He repeatedly fell asleep while being examined. No gross neurologic abnormality was elicited. The pupils were round and equal and measured about 3 mm. in diameter. The muscles of the iris contracted well to light and in convergence. There was no gross disturbance of the visual fields. No abnormal sweating or greasiness of the skin was seen.

Electroencephalographic Study. — It was difficult to obtain an electroencephalogram from this subject while he was awake. A short sample of record from the occipital region obtained in this state shows an excellent 9 to 10 waves per second (alpha) pattern (fig. 10 *A*). Waves characteristic of various depths of sleep dominate the record. Before hyperventilation, early sleep waves are seen (fig. 10 *B*). Almost immediately after the onset of hyperventilation sleep waves are replaced by prominent alpha sequences (fig. 10 *C*). During hyperventilation a short volley of approximately 5 per second, asymmetric waves is observed (fig. 10 *D*).

COMMENT

In 5 cases the classic syndrome of Gélineau (irresistible, inappropriate diurnal sleep and transient physical powerlessness under the influence of affective stimuli) was evident clinically. In the other 5 cases the isolated symptom of uncontrollable sleep was present.

An outstanding feature in this series of cases was the familial nature of the disorder. Five patients had a brother, a sister or a first cousin who was subject to a sleep disorder or to epilepsy. Two patients each had a sibling who was narcoleptic and a sibling who was epileptic. The strong familial characteristic observed in this series of cases is unique in the literature of narcolepsy.

Case 7, in which there was a history of a convulsive disorder in childhood, is similar to the case of Gowers, cited by Wilson.[1] Stuttering was a prominent characteristic in 3 cases. J. H. S. (case 10) stuttered as a prelude to the cataplectic component of his seizure pattern.

In 2 cases the onset of symptoms began after an attack of influenza. The latent periods from the infection to the appearance of the sleep disorder were three and five years respectively. In certain instances a head injury apparently acted as a catalytic agent to increase the intensity or frequency of the sleep seizures.

On gross neurologic examination scattered signs were recognized. In case 4 there was a strong possibility of trauma at birth. The presence of hypothalamic dysfunction was difficult to rule out in case 10.

The basic electroencephalograms, taken between intervals of "sleep," showed no wave pattern characteristic of the narcoleptic syndrome. The proportion of alpha frequencies varied from complete dominance to almost complete absence.

The abnormal wave forms observed in the majority of the records were similar, in all essentials, to those obtained from epileptic persons. The isolated bursts of high voltage, slow waves in the electroencephalograms of case 1 (fig. 1 *B*), case 2 (fig. 2), case 4 (fig. 4 *B*) and case 5 (fig. 5 *B*) all occurred within two to four minutes after the start of the recording. They were in no way associated with any clinical or electroencephalographic evidence of sleep. The record in case 6 (fig. 6) is an excellent example of the wave types encountered with certain of the epilepsies. The "epileptic" response to hyperventilation was noteworthy in case 9 (fig. 9 *C*) and in case 10 (fig. 10 *D*). Under the test conditions established, these responses were seldom seen in the absence of any gross change in the mechanisms or components of carbohydrate metabolism.[5] The establishment of a dominant rhythmic activity in a random frequency pattern during hyperventilation was observed in case 3 (fig. 3) and case 8 (fig. 8). This phenomenon has occasionally been recognized in other records low in alpha wave content. Whether the effect is due to an increase or a decrease in the several gaseous elements supplied to the brain or is the result of release of "alpha wave inhibition" by release of the subject's concentration on himself or the test cannot be definitely stated.

During the sleep stage of the narcoleptic seizure it has commonly been observed that the control electroencephalogram gives way to a pattern of low amplitude, high frequency waves, which is subsequently superseded by predominantly low frequency, high voltage volleys. These discharges are entirely similar to the wave sequences observed during physiologic sleep. The congruity of these observations makes it apparent that the sleep component of the narcoleptic seizure is fundamentally a manifestation of physiologic sleep, albeit inappropriate.

Moreover, the unanimity in the observation of "sleep waves" almost mandates the acceptance of the term hypnolepsy, at least to designate the sleep component of the narcoleptic syndrome. However, since the sleep component is so overwhelmingly the primary presenting complaint of

5. Davis, H., and Wallace, W. M.: Factors Affecting Changes Produced in the Electroencephalogram by Standardized Hyperventilation, Arch. Neurol. & Psychiat. **47**:606-625 (April) 1942.

the patient, it seems entirely appropriate, as Foote[6] suggested in 1886, to designate the entire syndrome as hypnolepsy.

CONCLUSIONS

In a majority, 8 out of 10, of this series of cases of narcolepsy wave forms similar to those most commonly observed with the epilepsies were present.

Because of the unanimous objective electro-encephalographic evidence that the primary component of the narcoleptic syndrome is a sleep phenomenon, it appears, despite the antiquity of the term narcolepsy, that the syndrome should be designated by the name of hypnolepsy (Foote[6]).

Since the electroencephalographic abnormalities observed during the interseizure phase of the hypnoleptic (narcoleptic) syndrome appear qualitatively similar to those associated with the epilepsies, it appears that Wilson's concept that the narcoleptic (hypnoleptic) syndrome is a member of the family of epilepsies is confirmed. A more precise statement of this relationship, based on electroencephalographic evidence, is that the clinical manifestations both in the epilepsies and in hypnolepsy are often associated with objective evidence of disturbances in the physiology of the brain.

6. Foote, A. W.: Narcolepsy, abstracted, Lancet **1**:25, 1887.

ACETYLCHOLINE TREATMENT OF SCHIZOPHRENIA

LOUIS H. COHEN. M.D.; THOMAS THALE, M.D., AND MORRIS J. TISSENBAUM, M.D.

NORWICH, CONN.

The chief purpose of this paper is to report on the striking amelioration of a patient's schizophrenic illness following the administration of acetylcholine. The circumstances of the remission. if only in 1 case. seem to deserve report since their drastic and near catastrophic nature may throw some light on the mechanism of remission, not only with acetylcholine but possibly with other forms of shock therapy. The paper is also concerned with the effects of treatment with acetylcholine on 10 other patients with schizophrenia.

NEUROPHYSIOLOGIC EFFECTS OF ACETYLCHOLINE

Acetylcholine has been shown to have a stimulating effect at the myoneural junction. the parasympathetic endings. the sympathetic and parasympathetic ganglia and the cerebral cortex.[1] Intravenous injection of the drug in human beings is followed by convulsions associated with temporary cardiac arrest. In 8 epileptic patients Henderson and Wilson[2] observed various individual responses, namely, nausea, vomiting, intestinal peristalsis, sweating, changes in heart rate and fall in rectal temperature, immediately after cerebral intraventricular injection; other changes, which were not prominent, were flushing. sleep, variations in blood pressure, respiratory and pupillary changes, salivation and lacrimation. No motor phenomena were reported to have been produced in any patient.

The effect of acetylcholine on the blood vessels is of particular clinical interest because of the importance of vascular changes in production of neurophysiologic alterations. Wolff[3] observed that acetylcholine dilates the cerebral blood vessels; his studies have furnished the basis for the use of this drug in the treatment of epilepsy, though without success (Lloyd[4] and McLaughlin[5]). Electrocardiographic studies by Harris and Pacella[6] on psychotic patients clearly demonstrated bradycardia and cardiac arrest. Cardiac and respiratory irregularities and changes in blood pressure were reported (Bernheim and Bernheim[7]); it has been said that the respiratory changes are due to stimulation of chemoreceptor zones in the carotid sinus and the aortic arch and the inhibition of breathing partially to the effect of the drug on the respiratory center and the spinal cord (Schweitzer and Wright[8]). Gesell and Hansen[9] showed that slow intravenous injection of acetylcholine produced strengthening followed by weakening of respiration; abdominal, costal and accessory respiratory activities were affected independently.

The electroencephalographic observations include the demonstration of increased electrical activity of the cortex in the cat (Brenner and Merritt[10]) and in the rabbit (Miller, Stavraky and Woonton[11]). On the other hand, no electroencephalographic changes in the cat were observed by Chatfield and Dempsey[12] with acetylcholine alone, although specific changes were

1. Sollmann, T.: A Manual of Pharmacology, Philadelphia, W. B. Saunders Company, 1936, pp. 338-340.

2. Henderson, W. R., and Wilson, W. C.: Intraventricular Injection of Acetylcholine and Eserine in Man, Quart. J. Exper. Physiol. 26:83, 1936.

3. Wolff, H. G.: The Cerebral Circulation: XI. The Action of Acetylcholine, Arch. Neurol. & Psychiat. 22:686 (Oct.) 1929.

4. Lloyd, J. E. S.: Acetylcholine Therapy in Epilepsy, Brit. M. J. 1:999, 1933.

5. McLaughlin, F. L.: Acetylcholine in Treatment of Epilepsy, Brit. M. J. 1:997, 1933.

6. Harris, M. M., and Pacella, B. L.: Convulsant Shock Treatment of Patients with Mental Disease by Intravenous Injection of Acetylcholine, Arch. Neurol. & Psychiat. 50:304 (Sept.) 1943.

7. Bernheim, F., and Bernheim, M. I. C.: Action of Drugs on the Choline Esterase of the Brain, J. Pharmacol. & Exper. Therap. 57:427, 1936.

8. Schweitzer, A., and Wright, S.: Action of Prostigmine and Acetylcholine on Respiration, Quart. J. Physiol. 28:33, 1938.

9. Gesell, R., and Hansen, E. T.: Eserine, Atropine and Nervous Integration, Am. J. Physiol. 139:371, 1943.

10. Brenner, C., and Merritt, H. H.: Effect of Certain Choline Derivatives on Electrical Activity of the Cortex, Arch. Neurol. & Psychiat. 48:382 (Sept.) 1942.

11. Miller, F. R.; Stavraky, G. W., and Woonton, G. A.: Effects of Eserine, Acetylcholine and Atropine on the Electrocorticogram, J. Neurophysiol. 3:131, 1940.

12. Chatfield, P. D., and Dempsey, E. W.: Effects of Physostigmine and Acetylcholine on Cortical Potentials, Am. J. Physiol. 135:633, 1942.

171

produced when acetylcholine and prostigmine were applied together. In psychotic patients Harris and Pacella [6] demonstrated abnormal, slow and high potentials which they asserted were a result of the vascular changes induced by primary cardiac arrest. This conclusion opposed the contention of Brenner and Merritt,[10] who stated that acetylcholine produces characteristic cerebral electrical response "by direct action on the nerve cells, fibers or synapses of the cortex." So-called epileptic discharges were reported by Williams [13] in epileptic patients, but "no charges of an epileptic character" were observed in normal persons.

ACETYLCHOLINE IN TREATMENT OF MENTAL DISEASE

In a search for convulsant drugs the efficacy of which would not be mitigated by the complications attending other shock therapies, notably fractures, Fiamberti [14] described his observations on acetylcholine. A report by Borgarello [15] indicated the usefulness of acetylcholine in insulin treatment in the presence of diminishing insulin resistance in some patients. Sandri [16] observed that in patients treated with acetylcholine there is a tendency to an increased sodium and a decreased magnesium content of the blood. The recent paper by Harris and Pacella [6] reported the therapeutic effects of acetylcholine on 8 patients, 6 women and 2 men. They were given from 3 to 61 treatments, with convulsant doses ranging from 220 to 600 mg. The investigators found that there was no ameliorating effect on the mental condition and concluded that this form of therapy "does not appear to be a desirable procedure." One patient made a prompt recovery after a course of a few electric shock convulsions, which were administered after an unsuccessful course of 31 injections of acetylcholine. No ill effects were observed even with large doses.

Our studies were carried out on 11 patients—7 women and 4 men. The injections of acetylcholine [17] were given

intravenously as rapidly as possible. The dose in the first injection was 100 mg., and the amounts of the subsequent injections were increased in units of 50 mg. until a convulsion was produced. There was no evidence of the development of tolerance to the drug; in fact, the dose was sometimes decreased during the course of treatment without impairment of the convulsant effect. Generally larger amounts were necessary to produce convulsions in men than in women, probably because of the difference in weight. It was not felt necessary or desirable to restrain the patient during the seizure because the convulsion seemed so much more mild than that induced by metrazol or the electric current.[18] All injections were given in the morning to fasting patients; flatulence was common after an injection; voiding occurred occasionally, but defecation never took place. Most of the patients were reluctant to be treated, and it may be of interest that the patients who were subsequently given electric shock treatment displayed greater cooperation during such therapy.

DESCRIPTION OF SEIZURE

The following description is based on 27 instances in which a dose of 400 mg. was given and the effects were noted at fifteen second intervals.

Seven to ten seconds after injection the patient assumed a sitting position, with the knees drawn up to the chest, the arms flexed and the head bent forward. There were repeated violent coughs, sometimes with flushing. Forced swallowing and loud peristaltic rumblings could be heard. Respiration at this time was labored and irregular. Because of the continuous cough, the respiratory rate could not be determined adequately.

The coughing abated as the patient sank back in the bed. Forty seconds after injection the radial and the apical pulse were zero and the patient became comatose. At this time the pupils were dilated and reacted poorly to light. The deep reflexes were hyperactive. On some occasions a Babinski sign could be obtained.

In forty-five seconds the picture had become one of opisthotonos, abduction of the thighs, plantar flexion of the feet and pronation of the forearms, with opposition of the thumb and partial flexion of the fingers. At this time there was a brief period of apnea in some cases. Lacrimation, profuse perspiration and borborygmi were prominent. While the hypertonic state was developing there were occasional random movements of the limbs, sometimes slow, sometimes choreiform. The position of the limbs could be changed with little difficulty, and the new positions were frequently maintained. The deep

13. Williams, D.: Effect of Cholin-Like Substances on Cerebral Electrical Discharges in Epilepsy, J. Neurol. & Psychiat. **4:**32, 1941.

14. Fiamberti, A. M.: Sul meccanismo d'azione terapeutica della "burrasca vascolare" provocata con derivati della colina, Gior. di psichiat. e di neuropat. **67:** 270, 1939; Accessi a carattere epilettico provocati con l'introduzione sottooccipitale di sostanze vasodilatrici, Riv. sper. di freniat. **61:**834, 1937.

15. Borgarello, G.: Acetilcolina e insulinoterapia, Schizofrenie (supp.) **7:**83, 1939.

16. Sandri, P.: Le variazioni del sodio e del magnesio del sangue nel trattamento convulsivante con acetilcolina della schizofrenie, Cervello **19:**64, 1940.

17. Dr. R. J. Floody, of Hoffmann-LaRoche, Inc., furnished the acetylcholine used in this investigation.

18. Atropine was kept on hand, but it was never used. One patient was given atropine ten minutes before the administration of acetylcholine, but no particular effect was observed.

reflexes were diminished or absent, and conjugate deviation was commonly observed. The deviation might be in any direction. The tonus then decreased, and the patient lay quietly in bed—cold, moist and gray.

In about ninety seconds flushing of the face marked the return of the pulse. The respiratory rate rose to 24 to 43 a minute. Coughing and gulping again became evident. Readings of the blood pressure obtained in the next minute or two showed an average fall in both the systolic and the diastolic reading of about 30 mm. (In 1 patient an increase in pressure was observed.)

Consciousness, as indicated by response to questions or by purposive activity, returned in one hundred and twenty-five seconds.

The patients tended to lie quietly in bed after the treatment. Sometimes they dozed lightly, but there was no evidence of stupor or confusion. Usually they could recollect the first phase of the reaction, and they complained of the early sensations of choking or burning in the throat.

In men a dose of 400 mg. did not usually produce a seizure of the severity seen in women.

RESULTS

The accompanying table presents the principal data concerning the 11 patients treated. All the patients were schizophrenic.

Data on Eleven Schizophrenic Patients Treated with Acetylcholine

Name	Sex	Age, Yr.	Duration of Illness	No. of Treatments	Outcome
F. B.	F	30	4 yr.	5	No change
J. H.	F	47	22 yr.	10	No change
E. K.	F	18	2 yr.	24	No change
M. B.	F	31	1 mo.	10	Slight improvement
L. G.	F	29	1 mo.	11	No change
R. S.	F	38	1 yr.	11	No change
M. Z.	F	40	3 mo.	19	Moderate improvement
J. M.	M	22	4 mo.	4	No change
M. O.	M	28	7 mo.	8	No change
B. K.	M	25	2½ yr.	3	No change
A. F.	M	36	4 mo.	4	Remission

From these data it can be seen that there were slight improvement in 1 woman, moderate improvement in another and complete remission in 1 man. In 8 patients no clinical change was observed; in 4 of these patients, to whom electric shock treatment has since been given, sufficient improvement has occurred to warrant their release from the hospital.

In the single patient in whom a remission occurred with acetylcholine, the effects were so striking that a more extensive presentation seems justified.

A. F., an Italian man aged 36, a mechanic by trade, got along moderately well financially until the onset of his illness. He was described as "temperamental," seclusive and sensitive. His intelligence quotient was 89, indicating dull normal intelligence. In January 1943 he began to complain that people were against him and that he was to be punished for something he had done. He became unusually quiet and seemed depressed; he could not sleep or eat and manifested marked indecisiveness. Hospitalization began in February 1943, with a clinical picture of persistent ideas of reference, delusions of persecution and auditory hallucinations. He made three suicidal attempts. In April 1943 he was transferred to the Norwich State Hospital. He manifested auditory hallucinations, insisting that he could hear the voice of Christ continuously telling him where he had been wrong in the past. He said that people knew all about him, especially about his previous perverse sexual acts, and expressed many ideas of guilt and sin. He was suicidal and made several impulsive attempts to kill or injure himself, such as butting his head against the wall or through a window.

Electric shock therapy was begun on April 19. A total of 24 treatments was given, the course being completed on June 11. At the end of the course of treatments no improvement was evident, although he seemed quieter and more cooperative. The same delusions and hallucinations were present. On June 22, eleven days after the completion of the electric shock course, he impulsively pushed his head through a window pane, sustaining a deep laceration of the chin. He explained that a voice had told him to do this. Treatment with acetylcholine hydrochloride was begun on July 17.

Acetylcholine Therapy.—The patient had four treatments, with increasing doses, as follows:

Date	Dose, Mg.
7/17	150
7/21	300
7/23	450
7/27	600

The usual minor responses were noted during the first two treatments. He was pulseless for twenty seconds during the third treatment, with some twitching. The fourth treatment is summarized as follows:

Fourth Treatment (7/27/43): The patient was apprehensive before the injection of 600 mg. of the drug at 9 a. m. A few seconds (two or three) after injection coughing, gasping (air hunger [?]), restless activity and twitching occurred. He became comatose, and the pulse was not obtainable for fifty seconds during this period. The blood pressure was 134 systolic and 88 diastolic. The pulse returned, and the pupils were noted to be contracted. He was heard to mumble some religious phrases. After twenty seconds he again became pulseless, this time for two minutes and twenty seconds. During this period the patient became very pale (grayish) and rigid for about half a minute; there then occurred a brief period of relaxation, followed suddenly by convulsive movements with opisthotonos lasting about a minute, during which he was first flushed and then cyanotic. The pupils were dilated. Toward the end of this phase the patient again became limp and pallid; the pulse then returned for five seconds, after which he was again pulseless for fifty seconds. During the next three minutes the pulse rate was as follows:

First minute	42
Second minute	52
Third minute	80

At this time there occurred much salivation and sweating, and breathing was so difficult that use of the accessory respiratory muscles was obvious. The blood pressure was 182 systolic and 110 diastolic. There was much gasping and moaning, but the comatose state persisted for approximately one hour. The pupils remained dilated for about forty minutes, with no reactivity to light. Toward the end of this phase the patient became extremely restless and made wild, incoordinated movements and many loud, unintelligible outcries, such as one often sees during hypoglycemic coma (insulin shock). There was no further salivation or sweating.

At 10:15 a. m., 50 cc. of 50 per cent dextrose was given intravenously, with no response. The patient remained unconscious. He began to regain consciousness at about 10:45 a. m. and seemed fully awake by noon. He said that he felt weak, but he was ambulatory by late afternoon. There was complete amnesia for the entire episode.

From the time of this treatment the patient persistently denied having any hallucinations or delusions. For a short time he continued to be somewhat preoccupied with matters pertaining to religion, as shown chiefly in his letters home. He became increasingly cheerful and optimistic about the future and spoke freely of having had "a lot of foolish ideas and imaginations." The complete amnesia for the last treatment continued, although he remembered well the apprehension and malaise associated with the previous treatments.

In late August he was allowed to go home for a week's visit. His family was much impressed by his condition and insisted that he had not been so well for over a year. They requested his release. By this time the patient's religious notions seemed to be no different from what one would expect of an average devout Catholic. When the patient was released, on September 15, he seemed entirely free from symptoms.

COMMENT

The value of a therapeutic agent depends on its efficacy and its safety as compared with other agents used for the same purpose. Considerable data are now available in the literature on the efficacy and safety of the insulin, metrazol and electric shock procedures; fewer data are available on picrotoxin, nikethamide and camphor. Gellhorn [19] suggested that the autonomic nervous system is chiefly concerned in the various forms of shock therapy. Our data, pertaining to the effect of acetylcholine on 11 patients, can be added to those gathered by Fiamberti [11] and by Harris and Pacella.[6] It is probably statistically unjustified to come to definite conclusions on the basis of so few cases, but it appears from the combined data that the relative therapeutic efficacy of acetylcholine therapy is slight and that its margin of safety may be relatively small. On the basis of our observations in 1 case the margin of safety between the convulsant and the lethal

dose appears rather narrow. Nevertheless, we would point out that in some of our patients a 600 mg. dose produced no alarming changes and that Harris and Pacella reported no ill effects.

The question of the underlying mechanism in production of clinical remissions arises again in connection with our observations. Granted that our data are concerned with only 1 remission, we cannot dismiss it as an "accident." Why is one form of treatment effective in a given patient when another is not? Harris and Pacella reported on a patient who had a remission with electric shock treatment after failure with acetylcholine, whereas 1 of our patients had a startling remission with acetylcholine after failure with electric shock. Furthermore, 4 of our patients underwent remission or improvement with electric shock after failure with acetylcholine therapy. One might say that we did not always give a sufficiently extensive course of acetylcholine treatments, but this criticism could not be made of the courses given by Harris and Pacella, with negative results.

We do not presume to answer these questions except to indicate that our experience with all forms of shock treatment over the past seven years leads us to the opinion that damage to the brain (of a reversible or an irreversible sort) occurs. We would include our experience with frontal lobotomy. The diffuse hemorrhagic lesions observed in the brains of patients who have died after shock treatment of any sort indicate that in all patients there is probably induced, at least to some degree, the same pathologic process. Even in those instances in which the damage is reversible, a modified neurophysiologic status is established.

Under such changed conditions the "clinical picture" changes, at least in the sense that the productive symptoms often disappear, if only temporarily. We have never observed any definite alteration of affective flattening in schizophrenic patients by shock treatment. The poor prognosis, despite treatment, in cases of long-standing disease is generally accepted. It is common knowledge that as affective deterioration progresses the productive symptoms (hallucinations, delusions, excitement, stupor) disappear and that the typical deteriorated patient is essentially free of such symptoms. Here one is confronted with the paradox that the patient is better when he is worse. We apply the same paradox to the effects of shock treatment: The damage to the brain, through change in the neurophysiologic pattern of the patient's experiencing, makes the production of certain psychotic symptoms and signs less likely, perhaps in some patients impossible.

19. Gellhorn, E.: Autonomic Regulations: Their Significance for Physiology, Psychology, and Neuropsychiatry, New York, Interscience Publisher, Inc., 1943, p. 305.

We incline to the opinion that the consequence of such cerebral damage is the "artificial" production of affective flattening. The data [20] on the quieting effect of shock treatment on excited and overactive patients would bear this out. It is probable that prolonged hypoxia is basic to the damage to the brain.[21]

We conjecture that the changes in the brain induced by prolonged cardiac arrest with acetylcholine were at the basis of our patient's remission. The drug, apparently, has no other virtues —a small one, obviously, in the light of the near catastrophic consequences. Nevertheless, the fact remains that an almost immediate remission was produced, a clinical effect which was not obtained in any other patient. We consider that extensive damage to the brain was done in this patient and not in the others, despite comparable doses. Furthermore, we consider that this cerebral damage was of such a sort that obvious schizophrenic symptoms, at least for the time being, are impossible.

SUMMARY

With 8 of 11 schizophrenic patients treated with convulsant doses of acetylcholine no general therapeutic benefit was obtained. In 1 patient there was slight, and in another moderate, improvement. One patient's condition underwent a dramatic remission after a therapeutic episode in which he was pulseless for such long periods that he was considered probably dead. On the basis of the available literature, it is considered that prolonged cardiorespiratory collapse occurred, as a consequence of which changes in the brain were produced.

The therapeutic results do not justify the continued use of acetylcholine in this manner, particularly since the margin of safety of the drug appears to be extremely slight.

Norwich State Hospital.

20. Cohen, L. H.: The Early Effects of Metrazol Therapy in Chronic Psychotic Overactivity, Am. J. Psychiat. 95:328, 1938. Androp, S., and Green, E.: Résumé of Metrazol-Shock Therapy in Schizophrenia, Dis. Nerv. System 2:222, 1941. Kubanck, J. L., and Ruskin, S. H.: Electrotherapy in Schizophrenia, J. Nerv. & Ment. Dis. 95:698, 1942. Cohen, L. H., and others: Frontal Lobotomy in the Treatment of Chronic Psychotic Overactivity, Psychosom. Med. 4:96, 1942. Reznikoff, L.: Comparison of Metrazol Convulsive Therapy with Electric Shock in Treatment of Schizophrenia, Arch. Neurol. & Psychiat. 49:587 (April) 1943.

21. Himwich, H. E., and Fazekas, J. F.: Factor of Hypoxia in the Shock Therapies of Schizophrenia, Arch. Neurol. & Psychiat. 47:800 (May) 1942.

EFFECT OF SERUM ON SURVIVAL TIME OF BRAIN TISSUE AND REVIVAL OF CEREBRAL OXIDATION

JOSEPH WORTIS, M.D.

NEW YORK

Clinical experience with the use of blood transfusions [1] in the relief of irreversible insulin coma suggested the possibility that cerebral oxidation—the term is here used to denote oxygen uptake—may at times be depressed or suspended in vivo through the depletion or destruction of certain substances, other than oxygen or dextrose, contained in whole blood. The following in vitro studies were undertaken therefore to test the effect of certain constituents of the blood on the respiratory activity and survival time of brain tissue and the revival of cerebral oxidation after its spontaneous depression. I at first hoped to imitate the hypoglycemic effect by allowing the tissues to exhaust their own intracellular stores of carbohydrate and then attempting to revive the diminished oxidation at various intervals thereafter by the addition of dextrose, whole blood or serum. In preliminary trials the tissues showed a striking capacity to maintain their oxidation even in a dextrose-free medium for six or more hours before the oxidation fell off sharply. It was by no means certain, however, that the flattening of the oxidation curve which then occurred could be attributed to exhaustion of substrate, for in spite of a greatly accelerated rate of oxidation the presence of 200 mg. of dextrose per hundred cubic centimeters of immersion fluid made relatively little difference in the survival time of the tissue, and determinations of dextrose in the immersion fluid made after oxidation had practically ceased revealed a large excess of dextrose still available. Nor could the depression of oxidation be attributed to the development of a toxic inhibiting factor, since oxidation was not revived after the tissues had been washed in isotonic solution of three chlorides U. S. P. and placed in a fresh suspension medium. Inclusion of a small amount of fresh serum (0.25 cc. in 3 cc. of immersion fluid) effectively prevented any flattening of the oxidation curve within the limits of the duration of the experiment, i. e., twelve hours. The details of these experiments will now be described.

This study was aided by a grant from the Warner Institute for Therapeutic Research.

From the Psychiatric Division of Bellevue Hospital and the Department of Psychiatry of New York University College of Medicine.

1. Wortis, J., and Lambert, R. H.: Irreversible or Hyperglycemic Coma, Am. J. Psychiat. **96**:335, 1939.

METHOD

Minced whole brain tissue of adult white rats (over 5 months old and weighing over 200 Gm.) was used. In almost all the experiments less than half an hour elapsed between the decapitation of the rats and the beginning of the experiment. From 40 to 70 mg. of the minced wet tissue was weighed and immersed in 3 cc. of freshly prepared Krebs-Ringer phosphate solution [2] buffered at a p_H of 7.38 with various concentrations of dextrose, as indicated later. In the tipping
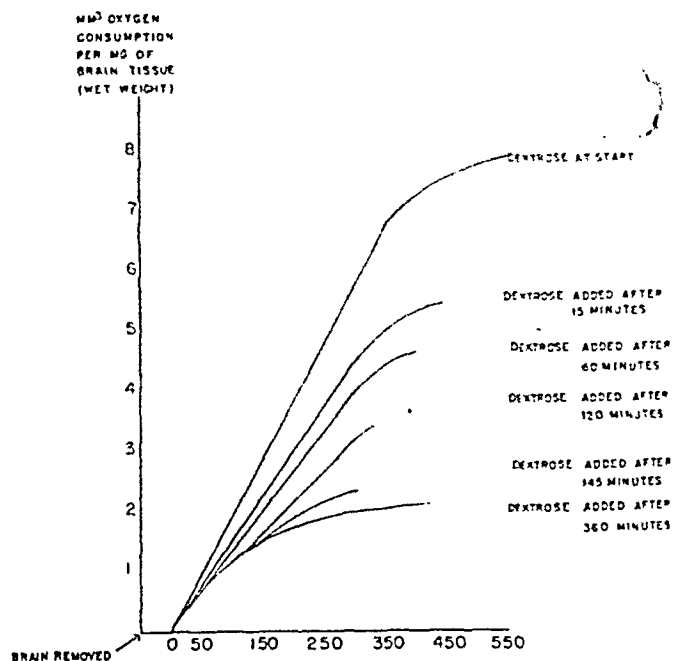
Fig. 1.—Effect of the addition of dextrose on the oxygen uptake of minced rat brain. Sufficient dextrose was added at each point to the dextrose-free suspension medium to bring the concentration of dextrose to 200 mg. per hundred cubic centimeters. There was no effective revival of oxidation after six hours.

experiments 2.5 cc. of immersion fluid was used in the main chamber with 0.5 cc. of additional solution in the side chamber containing enough dextrose to make a concentration of 200 mg. of dextrose per hundred cubic centimeters of immersion fluid after tipping. In the serum experiments 0.25 cc. of freshly prepared serum was added to 0.25 cc. of the Krebs-Ringer phosphate solution in the side chamber, or an equal amount was included in the central chamber at the start. Barcroft-Warburg manometers were used in a water bath at a temperature of 37 C. Strict cleanliness was observed, but a series of entirely aseptic experiments were included as controls, with the same results. Only occasional experiments in the twelve

2. The Krebs-Ringer phosphate solution has the following formula: sodium chloride, 90 Gm.; potassium chloride, 4.6 Gm.; calcium chloride, 3.6 Gm., and magnesium sulfate, 3.73 Gm., buffered with sodium phosphate and potassium acid phosphate.

176

hour runs were discarded because of contamination, signified by an extremely rapid oxygen uptake. The p_n was frequently checked, but no significant changes were observed. The data from each experiment involved readings from two to three manometers checked against at least two thermobarometers. All curves were based on averages from at least 10 such experiments.

RESULTS

The oxidation curve for minced brain in plain Krebs-Ringer phosphate solution flattened off in approximately six hours. The addition of dextrose to the suspension medium did not revive oxidation in the brain after this period. The addition of dextrose at various intermediate intervals resulted in an increased rate of oxygen uptake and longer survival of the tissue, in direct relation to the time that had elapsed before dextrose was added (fig. 1). If dextrose was present at the start, the rate of oxidation was almost doubled and the survival time prolonged several hours. Between the sixth and the ninth hour, however, an abrupt flattening of the oxidation curve took place, and the tissues died. This abrupt flattening did not occur (fig. 2) if a small amount of serum (0.25 cc.) was present in the suspension fluid, but oxidation continued at a
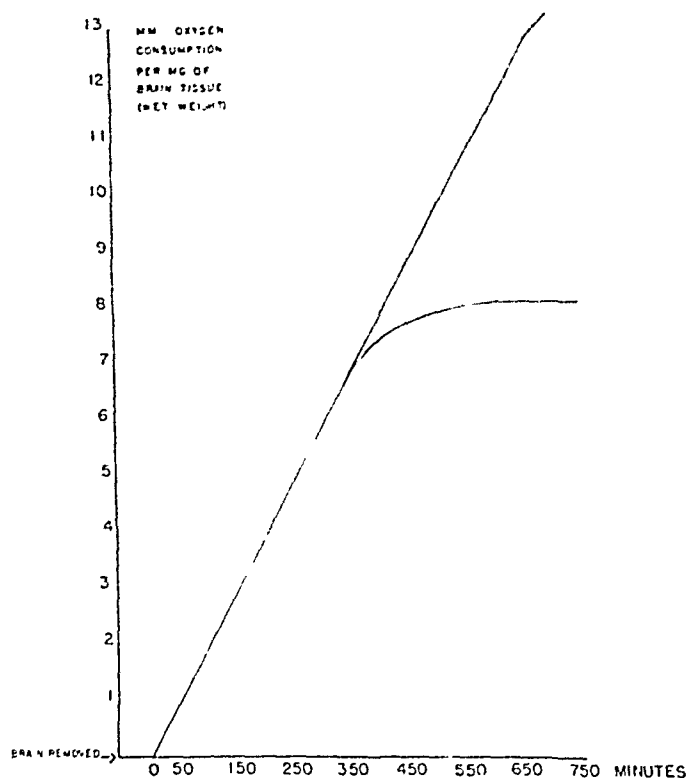
Fig. 2.—Two superimposed curves, showing the course of the oxygen uptake of minced rat brain with and without the presence of a small amount (0.25 cc.) of serum in 3 cc. of suspension medium containing 200 mg. of dextrose per hundred cubic centimeters. In the presence of serum, oxidation was maintained at a practically constant rate for the duration of the experiment (twelve hours).

practically constant rate for the duration of the experiment (twelve hours). In a dextrose-free medium the addition of a small amount of

rat serum (0.25 cc.) at the end of six hours served to support the flagging oxidation and to promote the survival of the tissue (fig. 3). This effect was not enhanced by the addition of dextrose to the serum or by the use of whole blood.

COMMENT

The demonstration of the superior advantages of serum over Krebs-Ringer phosphate solution
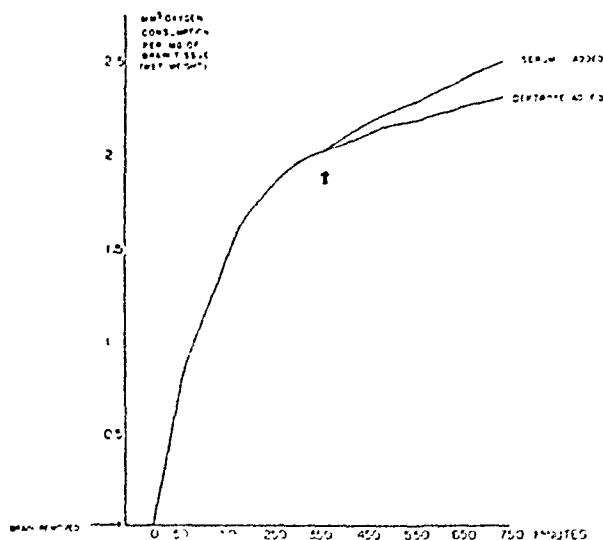
Fig. 3.—Effect of addition of a small amount (0.25 cc.) of serum to a dextrose-free suspension of minced adult rat brain. The addition of dextrose did not support the flagging oxidation. The addition of serum, of serum plus dextrose or of whole blood had the same effect in supporting the flagging oxidation.

as a medium for surviving tissues is not new and would make no claim to attention if the experiments did not serve to clarify some points in connection with the phenomenon. It is noteworthy that the presence of a small amount of serum in a dextrose medium did not accelerate the rate of oxidation, but greatly prolonged the maintenance of the metabolic activity of the tissue.

The apparent revival of flagging oxidation demonstrated in figure 3 is a similar phenomenon, for close analysis of the curves reveals that it is maintenance, rather than revival, of oxidative activity which is effected by the addition of serum. The possible explanations of the phenomenon are few: The amount of dextrose present in the serum cannot be considered a factor, and there is only the tenuous possibility that some other substrate is present in amounts sufficient to influence the metabolism of the tissues. A more likely possibility appears to be the presence in the serum of some essential element of the oxidative enzyme or catalyst system which is depleted or destroyed in the ordinary immersion fluid. Shaffer, Chang and Gerard [3]

3. Shaffer, M.; Chang, T. H., and Gerard, R. W.: The Influence of Blood Constituents on Oxygen Consumption in Nerve, Am. J. Physiol. **111**:697, 1935.

suggested some time ago that the large protein molecule of the serum served to maintain the normal permeability of the cell membrane.

The data of the experiments, together with clinical experience in the use of transfusions in cases of irreversible coma, may serve to throw light on the usefulness of serum in the revival of the flagging metabolism of the brain in some types of coma. It justifies further therapeutic trial with transfusions of serum or plasma in various nonspecific forms of coma, such as those seen after profuse hemorrhage, asphyxiation, carbon monoxide poisoning or vascular collapse.

SUMMARY AND CONCLUSION

The oxygen uptake of minced brain in plain Krebs-Ringer phosphate solution buffered at a p_H of 7.38 was approximately 0.85 cubic millimeters per milligram of tissue (wet weight) for the first hour, with a flattening off of the oxidation curve in approximately six hours. In a similar suspension medium of buffered Krebs-Ringer phosphate solution containing 200 mg. of dextrose per hundred cubic centimeters the oxygen uptake was 1.11 cubic millimeters per milligram of tissue for the first hour, with an abrupt flattening of the oxidation curve about eight hours afterward. This abrupt flattening did not occur if a small amount of serum was present in the immersion fluid, but oxidation continued at a practically constant rate for the duration of the experiment.

The cessation of oxidative activity of minced brain tissue was not due to lack of substrate, since determinations of the dextrose content of the immersion fluid revealed a substantial excess of dextrose still present after oxidations had practically ceased.

The addition of dextrose to a dextrose-free suspension medium did not revive oxidation in the brain after a period of six hours.

The cessation of oxidation in these experiments could not be attributed to the production of any inhibiting substance, since oxidation was not revived after the tissues had been washed in isotonic solution of three chlorides U. S. P. and placed in a fresh suspension medium.

There was a significant support of flagging oxidation on the addition of serum to a dextrose-free medium at the end of six hours. The effect was not enhanced by the combination with dextrose or by the use of whole blood.

The most likely explanation of the phenomenon appears to be the presence of some essential of the oxidative enzyme system in the serum or the restoration of normal osmotic relations by the large serum protein molecule.

50 Park Avenue.

INJURY TO THE PERONEAL NERVE DUE TO CROSSING THE LEGS

HENRY S. DUNNING, M.D.

NEW YORK

According to Spalteholz,[1] the common peroneal nerve usually branches from the sciatic nerve at the apex of the popliteal space. It runs along the medial margin of the biceps femoris muscle on the dorsal surface of the lateral head of the gastrocnemius muscle distad and laterad, and then behind the head of the fibula to the lateral margin of the shaft of the fibula, where it divides into its two terminal branches, the deep and the superficial peroneal nerve, both of which pass through the canal located in the origin of the peroneus longus muscle. The deep peroneal nerve innervates the tibialis anterior muscle and the extensor muscles of all the toes and supplies sensory fibers to the skin of the dorsal surfaces of the adjacent halves of the first and second toes. The superficial peroneal nerve innervates the peroneal muscles and supplies sensory fibers to the skin of the dorsal surface of the medial half of the big toe, of the dorsal surfaces of the adjacent halves of all the other toes, of the top of the foot and of the lower portion of the anterior surface of the leg. Dorsal flexion and eversion at the ankle and extension of all the toes are entirely dependent on these nerves.

Since the proximal portions of the deep and superficial peroneal nerves lie on the lateral margin of the shaft of the fibula and are covered only by a thin layer of soft tissue, they are vulnerable to injury by pressure. Persons who sit with their legs crossed in such a manner as to allow the upper third of the shaft of the fibula of the uppermost leg to ride against the head of the fibula of the lowermost leg commonly experience numbness and tingling on the top of the foot of the uppermost leg, due to compression of the superficial peroneal nerve between the two bones. Wilson[2] stated that, in spite of the frequency with which such sensations are produced in the leg or foot by sitting in a cramped way or with the legs crossed, reports of sleep palsies of the leg muscles due to nerve compression are rare as compared with similar injury to the radial or the ulnar nerve. The following case is an instance of bilateral injury to the peroneal nerve by habitual crossing of the legs.

REPORT OF A CASE

A physician aged 65 consulted me on June 29, 1942, complaining of foot drop on the left. He stated that five weeks previously, on his rising to his feet after reading in the sitting posture with his legs crossed, he had noted a sensation of numbness of the top of the foot and of the lower portion of the anterior surface of the leg on the left. Later that day the left foot began to slap the floor when he walked. Weakness at the left ankle increased, and several days later he almost fell down stairs when he turned his left ankle. Weakness and the sensation of numbness persisted, and a few days prior to the consultation he found an area of numbness on the top of the right foot when he was drying it with a towel but noted no weakness at the right ankle.

1. Spalteholz, W.: Hand-Atlas of Human Anatomy, translated by L. F. Barker, ed. 5, Philadelphia, J. B. Lippincott Company, 1900-1903, vol. 3, p. 782.

2. Wilson, S. A. K.: Neurology, edited by A. N. Bruce, Baltimore, Williams & Wilkins Company, 1940, vol. 1, p. 345.

Fig. 1.—Photograph of the patient in his usual sitting posture, with the upper third of the shaft of the left fibula riding against the head of the right fibula. The areas of impaired sensation are outlined.

Fig. 2.—Photograph of the patient's legs, showing a dark area of skin over the upper third of the shaft of each fibula caused by the long-standing pressure.

Neurologic examination revealed abnormal signs only in the legs. The left foot slapped the floor when the patient walked. There was considerable weakness in dorsal flexion and in eversion at the ankle and in extension of all of the toes on the left. Fascicular twitchings were seen in the anterior muscles of the lower portion of the left leg. No weakness of the right leg could be found. There was no muscular wasting, and the knee, ankle and plantar reflexes were normal. Sensation to light touch and pinprick was decreased in the areas outlined in figure 1. Vibratory sense was also diminished over the left external malleolus.

The signs were clearly those of bilateral dysfunction of the peroneal nerve. On the left the deep and superficial branches of the common peroneal nerve were involved; on the right only the superficial branch was affected. Examination of the skin revealed an area of brownish induration, in which the hairs had been broken off short, over the upper third of the shaft of each fibula, indicating long-standing pressure directly over the proximal portions of the terminal branches of the common peroneal nerves. These cutaneous lesions are illustrated in figure 2. The patient stated that he had always sat with his legs crossed, more often with the left leg over the right than vice versa. At times he had noted that a foot had "gone to sleep." Figure 1 demonstrates his usual sitting posture, with the upper third of the shaft of the left fibula riding against the head of the right fibula. He explained that early in June 1942 he had taken some examinations, for which he had prepared continuously for six months. During this period he had spent three to four hours daily reading in the sitting posture with his legs crossed. Garters had not been worn during the last two months.

The patient was advised to stop crossing his legs and did so. Improvement was continuous. Six weeks later his gait was entirely normal. When he was last seen, about three months after the first examination, there was barely perceptible weakness in dorsal flexion and in eversion at the ankle and in extension of the big toe on the left, and the areas of impaired sensation had receded about four fifths of their original size. The marks of pressure on the legs had almost disappeared.

CONCLUSION

The almost universal habit of sitting with the legs crossed may cause injury to the peroneal nerve.

525 East Sixty-Eight Street.

PROGRESSIVE MULTIFORM ANGIOSIS

ASSOCIATION OF A CEREBRAL ANGIOMA, ANEURYSMS AND OTHER VASCULAR CHANGES IN THE BRAIN

SILVANO ARIETI, M.D., AND EDWARD W. GRAY, M.D.

BRENTWOOD, N. Y.

Knowledge of the growths originating from the blood vessels of the brain is still limited and confused. No doubt the monograph of Cushing and Bailey [1] and other recent works (Bergstrand,[2] Northfield [3]) have helped greatly to clarify this interesting chapter of neuropathology. However, the relative rarity of these conditions also limits their study, so that further contributions have to be anticipated. This consideration justified in our opinion the report of a case presenting a cerebral angioma, a huge aneurysm of the circle of Willis, diffuse alterations of the subarachnoid vessels and an aneurysm of the abdominal aorta. It was felt that the study of this peculiar association could throw additional light on the subject.

REPORT OF A CASE

History.—The family history was without significance. The patient was born in 1884 in the United States, of Irish-American parentage. No disturbances of behavior or neurotic traits were present during childhood. At the age of 12 years he was struck on the head with the shaft of a wagon. No details are available concerning either the immediate result or the after-effect of the injury. At the age of 17 he began to have convulsions, on the average of two or three a year. At the age of 28 he started to drink and since then had had several attacks of dipsomania. In July 1936 he began to drink even more excessively. He had occasional visual hallucinations and borrowed money from his friends and neighbors, spending all he could get his hands on for alcohol.

Examination on Admission.—The patient was admitted to Pilgrim State Hospital on Sept. 28, 1936 on account of addiction to alcohol and disorderly behavior. Physical examination on admission revealed slight enlargement of the heart and chronic bronchitis.

1. Cushing, H., and Bailey, P.: Tumors Arising from the Blood Vessels of the Brain: Angiomatous Malformations and Hemangioblastomas, Springfield, Ill., Charles C Thomas, Publisher, 1928.

2. Bergstrand, H.: On the Classification of the Haemangiomatous Tumours and Malformations of the Central Nervous System, Acta path. et microbiol. Scandinav., 1936, supp. 26, pp. 89-95.

3. Northfield, D. W. C.: Angiomatous Malformations of Brain, Guy's Hosp. Rep. **90**:149-170, 1940-1941.

The pupils reacted sluggishly to light. The knee jerk was diminished and the ankle jerk absent on both sides. Routine laboratory tests gave normal results. The Wassermann reaction of the blood was negative. Nothing outstanding was noted in examination of the mental status. Behavior and mood were not disturbed. No delusional or hallucinatory material could be elicited. The patient was well oriented as to time, place and person; memory was excellent, and retention and immediate recall were good when he made a real effort. His intelligence was average. The diagnosis was "psychosis due to alcohol, confusional syndrome." About a month later he was paroled. No epileptic seizures occurred in this period.

Subsequent Course.—The patient was returned to Pilgrim State Hospital in January 1937 with a history of having started to drink heavily after New Year's. He again made a satisfactory adjustment in the hospital and was paroled in July 1937. After this, for about three years, he was in and out of the hospital several times. In April 1938 paralysis of the left superior rectus and left inferior oblique muscles was observed.

The patient's last admission was in April 1940. At that time examination of the eyegrounds revealed bilateral optic nerve atrophy, and the visual fields showed bilateral nasal hemianopsia. Since then the patient had had seizures at irregular intervals, and his mental status had deteriorated steadily. On account of increasing weakness, he was put to bed on Feb. 10, 1943. On the evening of March 10 he had three grand mal attacks. He remained in an unconscious state the following day, then rallied to a point where he was able to take some fluid and to speak to relatives who came to see him. The temperature ranged from 101 to 104 F. The pulse rate varied from 90 to 120 and the respiratory rate from 24 to 32 per minute. The signs in the chest were consistent with a diagnosis of bronchopneumonia.

On March 15 he lapsed again into coma and died at 5:40 a. m.

Necropsy.—Brain: The brain weighed 1,630 Gm. Nothing unusual was noticeable on the external surface of the dura. On removal of the dura no clouding of the leptomeninges was apparent except for a local area, to be mentioned later. The convolutions showed no appreciable change. It was observed that the blood vessels over the surface of both hemispheres were enlarged, thickened and much more prominent than usual (fig. 1). In certain areas they appeared to be increased not only in volume but in number. It was often difficult to determine the nature of these vessels. In the frontal lobe, for instance, vessels which had the appearance of arteries opened instead into the superior longitudinal sinus. At the terminal part of the left lateral cerebral fissure one noted two large, thickened vessels, which were directed toward the superior

parietal lobule (fig. 2). The most anterior of these two blood channels was located immediately caudal to the posterior central gyrus; the posterior vessel ran through the supramarginal gyrus and the angular gyrus and finally reached the superior parietal lobule, near the transverse occipital sulcus. In the superior parietal lobule these two vessels gave off minor branches in such numbers as to constitute a true
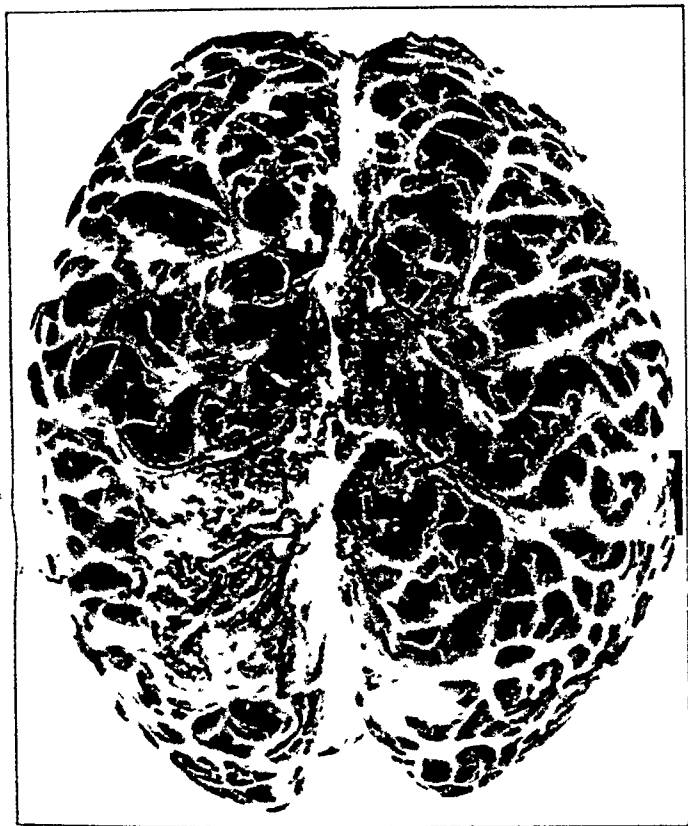
Fig. 1.—Dorsal view of the brain. All the vessels are enlarged and thickened. Note the angioma on the left parietal lobe. (A thickening of the arachnoid limits there the visibility of individual vessels.)
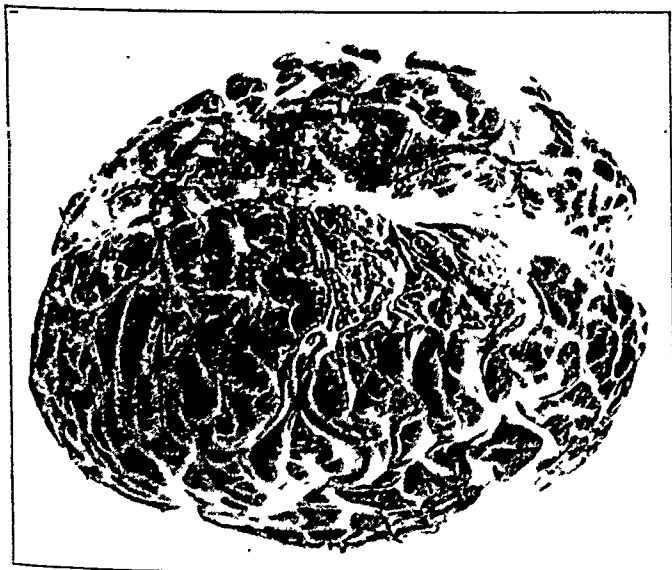
Fig. 2.—Left oblique view of the brain. Two large ascending vessels give rise to the angioma in the left parietal lobe (described in the text).

angioma. The vessels of the angioma had a tortuous and interwoven course. This network covered the entire surface of the lobule and expanded medially into the precuneus. The arachnoid covering the angioma was thickened and clouded, so that the visibility of the individual vessels was limited' (figs. 1 and 2).

When the brain was cut in coronal sections, it was noted that the lesion projected deep into the parietal lobe (fig. 4A). It measured 5 by 3.5 by 3.8 cm. In the vicinity other, small clusters of enlarged vessels appeared in the subarachnoid space.
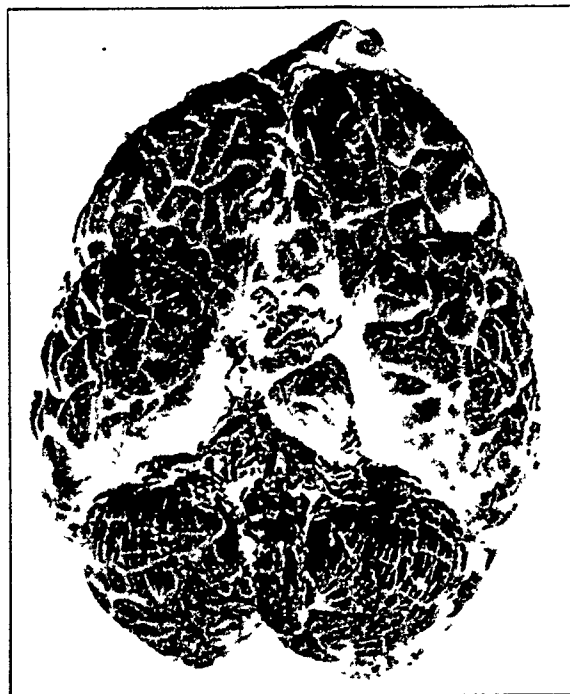
Fig. 3.—Ventral view of the brain, showing a large aneurysm. (The incisions in the aneurysm were made at necropsy.)
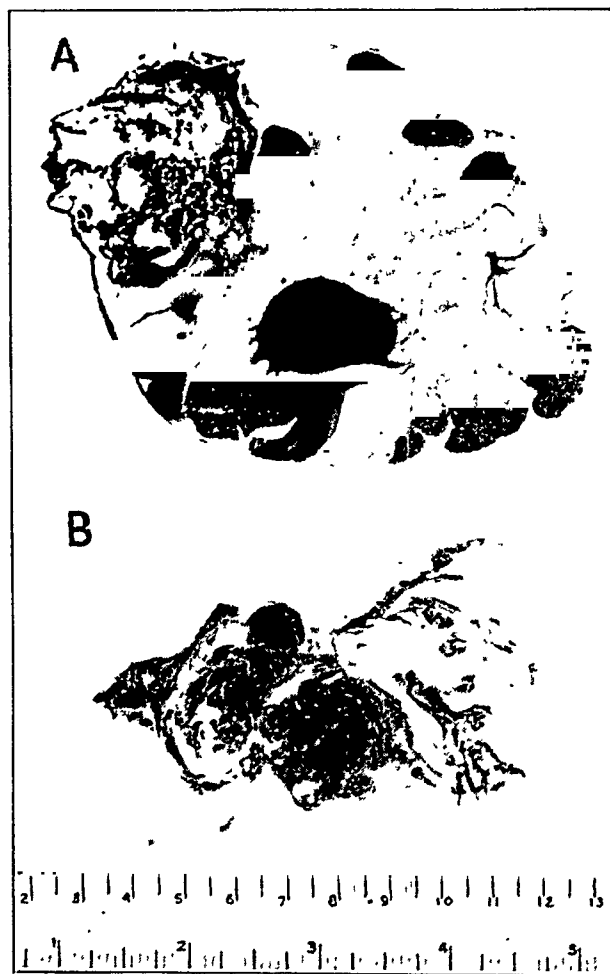
Fig. 4.—A, frontal section of the left parietal lobe passing through the center of the angioma. B, aneurysm after removal from the brain.

On the basal aspect of the brain an aneurysmal dilatation was noted on the left side of the circle of

Willis (fig. 3). This aneurysm was remarkably large and included the posterior communicating artery and short portions of the posterior cerebral and internal carotid arteries on the same side. Its anteroposterior perforate substance and the left half of the pons. The basilar artery was not involved. When the aneurysm was isolated (fig. 4 B), its surface was seen to be divided in two masses by a sulcus, which probably

Fig. 5.—General view of the central part of the angioma. Hematoxylin and eosin; × 25.

Fig. 6.—A (× 55), gigantic vessel, showing splitting of the elastica. B (× 25), enormous vessel, showing varied appearance of the elastica, which at certain points maintains the normal escalloped aspect and at other shows a more or less rectilinear course of splitting. Weigert stain.

diameter was about 5 cm. and its transverse diameter about 3.5 cm. It compressed the optic -chiasm, the mamillary bodies, the cerebral peduncles, the posterior corresponded to the junction of two vessels. The larger of these masses was the caudal and the smaller the frontal portion. Dorsal to the caudal mass was a

third, small, spherical mass. Section of the aneurysm revealed that it was completely occluded by a thrombus. The entire aneurysm had a capacity of 27.5 cc., as measured by the volume of replaced water.

Other Organs: Many areas of consolidation were noted in both lungs. There was an aneurysm, measuring 4 cm, in the abdominal aorta. An undescended testicle was observed in the abdomen.

Microscopic Examination.—Angioma: Hematoxylin and eosin preparations of sections from the lesion in

zones, in particular where meningeal tissue was recognizable.

The large vessels presented the most irregular forms, with constrictions and dilatations. Projections of the wall into the center of the vessels were as frequent as outward projections. Aneurysmal outpocketings of the vessels were also frequently observed. The irregularities in the circumference of the blood channels were due either to the tortuous turning of the vessel or to the difference in thickness in various parts of the wall.

Fig. 7.—*A*, group of vessels, showing various stages of the process of arteriolization. *B*, course of the elastica, following the irregularities of the vascular wall. Weigert stain; × 55.

the left parietal lobe disclosed that it consisted of blood vessels and little interstitial tissue. The vessels seemed to originate in the subarachnoid space, dipping into the fissures and sulci which separate the cerebral convolutions. Because of their number and size, they compressed the convolutions in such a way as to leave little nerve tissue between the vessels from two neighboring sulci. The vessels were of various sizes and presented numerous irregularities. Many of them were gigantic and conferred to the tissue a cavernous aspect (fig. 5). Medium-sized vessels were less numerous. Capillaries and precapillaries were seen only in a few

Vessels of medium size presented the same irregularity of form, but less frequently and in a less pronounced manner.

The nature of the vessels was not always easy to determine in hematoxylin and eosin sections. In these preparations, however, the veins seemed to outnumber the arteries.

The intima presented various characteristics. At times it consisted of a single row of flattened cells, but as a rule it was conspicuously thickened. At times this intimal proliferation was equally pronounced throughout the circumference of the vessel, but oftener it was

particularly prominent in certain spots, forming the aforementioned nodules projecting into the lumen (fig. 8 *B*). Proliferation of the intima to such an extent as entirely to occlude the vessel was only exceptionally observed. The presence of swollen endothelial cells lining the lumen was noted frequently, and almost exclusively in veins (fig. 8 *A*). These swollen endothelial cells contained droplets of fat. In Van Gieson sections the thickened intima appeared to contain numerous collagen fibers. Weigert sections revealed the presence of an elastic interna in many vessels and

(fig. 7 *B*). Thickening of the elastica was frequently encountered, but far more frequent was the splitting of this membrane in several layers (fig. 6 *A* and *B*). Many vessels did not have a definite elastic membrane but showed numerous elastic fibers running concentrically in the intima. These fibers were often gathered together in certain points of the circumference and gave the impression of forming there a real elastic membrane (fig. 7 *A*). This phenomenon, referred to by many authors as a process of arteriolization, was frequently observed in this case. Not seldom, how-
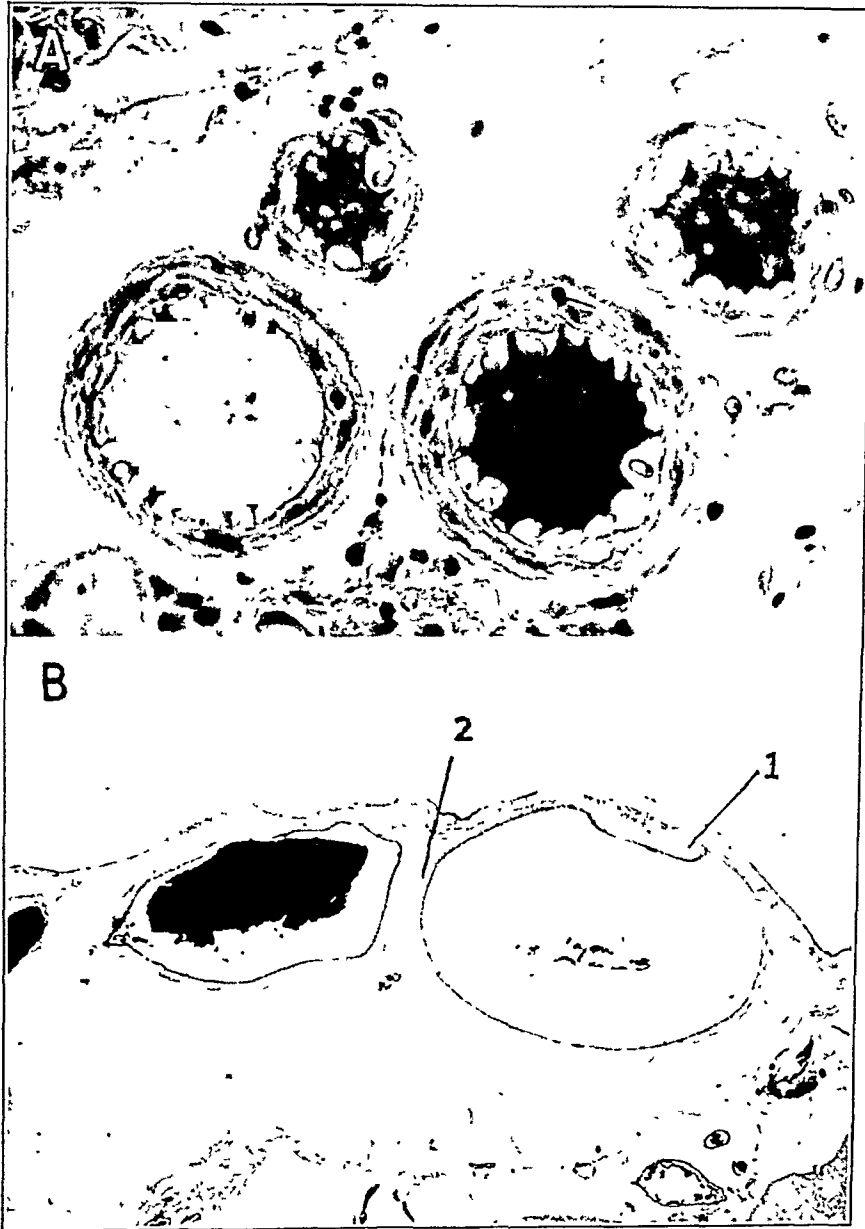
Fig. 8.—*1* (× 325), group of vessels, showing swelling of the intimal endothelial cells and projection into the lumen. *B* (× 5), enlarged subarachnoid veins of the right frontal lobe. Note two intimal thickenings of one vessel. At *1* the nodular thickening projects into the lumen; at *2* the thickening extends centrifugally. Hematoxylin and eosin stain.

established in this way the arterial nature of many blood channels which in hematoxylin and eosin preparations had the appearance of veins. In many vessels, especially those of medium size, the elastic membrane had the normal tortuous, escalloped appearance. In other vessels, especially those of gigantic size, the elastica had at times a relatively rectilinear course, probably due to lack of efficient contraction of the tunica media; at other times it was tortuous, following all the irregularities of the vascular circumference

ever, the elastic fibers were seen leaving the intima and invading the other coats. At times they were of such quantity that in Weigert sections the entire width of the three coats appeared as a network of elastic fibers. The media also appeared thickened. Often this tunica also participated conspicuously in the formation of the inward projections already described. Van Gieson and Mallory stains for connective tissue revealed the presence of smooth muscle cells in the media, but these muscular elements were by no means numerous.

Connective tissue, collagen and elastic fibers were the chief constituents of this tunica.

The adventitia appeared generally enlarged, but not so much so as the intima and the media.

Retrogressive and degenerative characteristics were not important features in the vascular elements of this lesion. Hyaline degeneration of the vascular walls was not seen. Calcification of the walls was observed in a few sections.

The interstitial tissue surrounding the vessels offered also several points for consideration. In the most superficial part of the lesion this tissue was seen as a continuation of the leptomeninges lining the cerebral cortex. As a matter of fact, a few typical psammoma bodies were observed in it. The connective tissue nature of this interstitial tissue was easily recognized in sections stained by Van Gieson's method and with Mallory's aniline blue. It consisted chiefly of fibro-

those described in the angioma. The vessels appeared almost always enlarged. The thickening of the walls was less conspicuous and more uniform than that in the vessels of the angioma. However, nodules of the media and intima, identical with those already described, were encountered, even in vessels located at a great distance from the angioma, such as those in the right frontal lobe (fig. 8 B). Another interesting characteristic was the larger proportion of veins to arteries than was observed in the angioma. As a matter of fact, Weigert sections did not reveal any elastic interna or traces of elastic tissue in a great number of these vessels.

Swelling of endothelial cells lining the lumen was observed in several vessels, especially the veins. A few vessels were occluded by thrombi which were undergoing organization. In rare cases recanalization was observed.
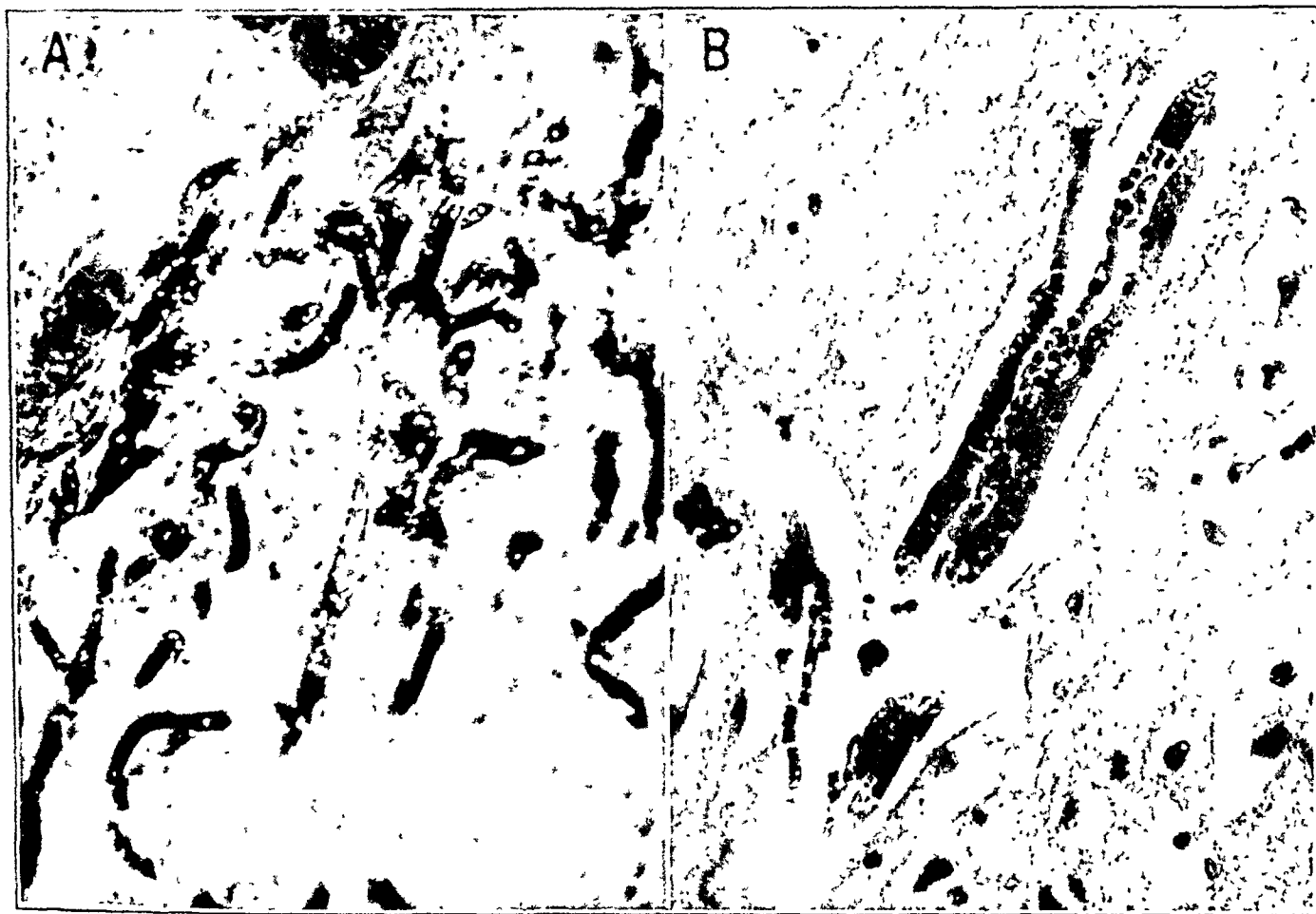
Fig. 9.—A (× 50), calcified cerebral capillaries; B (× 300), brushlike proliferation of cerebral capillaries. Hematoxylin and eosin stain.

blasts and collagen fibers. However, in the deepest salients of the lesion it was possible to distinguish two sharply differing components of the interstitial tissue —connective and glial tissue. The glial elements could be easily distinguished from the connective tissue in sections stained with Mallory's aniline blue. As already mentioned, normal parenchyma of the brain was seen between groups of vessels in the deepest part of the lesion. In this parenchyma calcification of capillaries was often observed (fig. 9 A). At times the calcification was advanced and involved the entire wall of the capillaries; often it was still incomplete, the capillaries appearing to be covered by numerous black dots.

Meningeal Vessels: Examination of the vessels lying in the subarachnoid spaces over all the lobes of the brain led to the conclusion that few vessels could be considered in normal condition. On the other hand, the vascular alterations were seldom as pronounced as

Cerebral Vessels: In most of the regions of the brain there were no appreciable vascular changes. On the other hand, in several areas an increased number of capillaries in the cortex and in the white matter was noted in hematoxylin and eosin sections. However, such an increase may have been more apparent than real and may have been due to the fact that the capillaries were engorged with blood and therefore much more apparent.

The Eros stain for vascular pattern[4] did not reveal any change in the network of capillaries in these areas, except for the occasional presence of brushlike formations of capillaries detached from a common trunk at an acute angle and running parallel with one another.

---

4. Eros, G.: Method for Fuchsin Staining of the Network of Cerebral Blood Vessels, Arch. Path. 31: 205-219 (March) 1941.

These brushlike formations, considered by Cerletti[5] as evidence of "absolute aggregate vascular proliferation" and interpreted in the same way by Eros and Priestman,[6] were at times so evident that even in hematoxylin and eosin sections they could be clearly seen (fig. 9 B). In a few areas, located in the vicinity of the angioma, groups of capillaries appeared calcified, as previously described.

Aneurysm: The walls showed great irregularity in thickness. It was not possible to recognize the three vascular coats. The walls consisted of connective tissue, and in some points of a homogeneous, hyaline-like structure. Calcareous deposits were frequently encountered. No remnants of elastic tissue were noted at any point in sections stained by the Weigert or other methods. No inflammatory changes were noted. The aneurysm contained an organizing thrombus.

COMMENT

The association in the same case of a cerebral angioma, diffuse vascular abnormalities in the brain, an aneurysm of the circle of Willis and an aneurysm of the abdominal aorta stimulates certain considerations. Such an association seems to substantiate the belief that the lesions were congenital and suggests the term malformations for the alterations described. However, careful examination and comparison of the intracranial lesions indicate that they were capable of modification and had acquired some neoplastic qualities. There is no doubt that the diffuse anomalies of the subarachnoid vessels and the angioma of the left parietal lobe had the same origin. However, the latter appeared to be at a much more advanced stage. The vessels of the angioma, although presenting qualitatively the same characteristics as the other subarachnoid vessels, were more enlarged and irregular, and the process of arteriolization had already taken place, or was taking place, in many of them. These observations indicate that the subarachnoid vessels, or group of vessels, probably would have formed other angiomas if the patient could have lived long enough. In addition, it seems that these lesions are not genuine static malformations but are capable of further development, differentiation and autonomous growth. We are therefore inclined to agree with Bergstrand,[2] who stated that the attempts to classify the vascular growths of the nervous system "as either tumours in the narrow sense or as malformations are bound to be misleading because the two conceptions do not exclude each other."

Although we agree with the statement of Turner and Kernohan[7] that the mode of progression of the angiomas is through enlargement of the individual vessels, we cannot agree with them in their assertion that this enlargement is due to static changes or to changes in the dynamics of the blood circulating through the vessels. The process of progressive arteriolization discloses that these vessels not only enlarge but differentiate. They seem, therefore, to have an inherent potentiality for development and growth.

The presence in this case of two aneurysms is of great interest and must be considered in relation to the pathogenesis of the condition. Tuthill[8] and McDonald and Korb[9] observed that such lesions are generally due to an arteriosclerotic process, and Maass[10] reaffirmed that their origin is to be attributed to a syphilitic infection. Eppinger,[11] as far back as 1887, noted that congenital structural defects are antecedent to formation of aneurysms. Forbus[12] attributed the formation of aneurysms to "weak spots," similar to those observed in the muscular coat of blood vessels in the brains of children. Globus and Schwab[13] expressed the opinion that inherent defects and superimposed acquired pathologic processes are complementary factors in the production of aneurysm. One of us (Arieti[14]) described a case of multiple meningioma associated with an intracranial aneurysm. We have recently observed a case in which an acoustic neurinoma and a popliteal aneurysm were presented. The last-mentioned observations[15] seem to support the view that often an ontogenetic defect is a fundamental factor in the formation of

5. Cerletti, U.: Die Gefassvermehrung in Zentralnervensystem, in Nissl, F., and Alzheimer, A.: Histologie und Histopathologie, Jena, Gustav Fischer, 1910, vol. 4, p. 77.

6. Eros, G., and Priestman, G.: Cerebral Changes in Carbon Monoxide Poisoning, J. Neuropath. & Exper. Neurol. 1:158-172 (April) 1942.

7. Turner, O. A., and Kernohan, J. W.: Vascular Malformations and Vascular Tumors Involving the Spinal Cord: A Pathologic Study of Forty-Six Cases, Arch. Neurol. & Psychiat. 46:444-463 (Sept.) 1941.

8. Tuthill, C. R.: Cerebral Aneurysms, Arch. Path. 16:630 (April) 1933.

9. McDonald, C. A., and Korb, M.: Intracranial Aneurysms, Arch. Neurol. & Psychiat. 42:298-328 (Aug.) 1939.

10. Maass, U.: Die Syphilis als häufigste Ursache der Aneurysmen an der Gehirnbasis, Beitr. z. path. Anat. u. z. allg. Path. 98:307-322, 1937.

11. Eppinger, H., cited by Globus and Schwab.[13]

12. Forbus, W. D.: On the Origin of Miliary Aneurysms of the Superficial Cerebral Arteries, Bull. Johns Hopkins Hosp. 47:239-284 (Nov.) 1930.

13. Globus, J. H., and Schwab, J. M.: Intracranial Aneurysms: Their Origin and Clinical Behavior in a Series of Verified Cases, J. Mt. Sinai Hosp. 8:547-578 (Jan.-Feb.) 1942.

14. Arieti, S.: Multiple Meningioma and Meningiomas Associated with Other Brain Tumors, J. Neuropath. & Exper. Neurol., to be published.

15. Eppinger.[11] Forbus.[12] Globus and Schwab.[13] Arieti.[14]

aneurysms. At times this defect may be considered responsible for associated lesions, such as tumors. This point of view is corroborated by the observations in this case. As a matter of fact, it is almost impossible to explain the association of two aneurysms with the other vascular lesions as purely coincidental. On the other hand, it seems logical to attribute all the lesions to one ontogenetic disorder, which in this case was limited strictly to the vascular system.

The lesions in this case having all been recognized as expressions of a pathologic entity, the problem is now to determine whether this picture can be included in the present classifications of the vascular disorders. As a matter of fact, the term angioma arteriovenosum would refer only to the lesion of the left parietal lobe. The term angiomatosis, used by Lévy,[16] Panara [17] and others, although including the angioma and the other alterations of the subarachnoid vessels, would not include the aneurysms. We cannot consider this case as representing a form, even abortive, of Sturge-Weber disease, if we accept the definition of this disease given by Bergstrand [2] and Northfield.[3] The condition can by no means be identified with Lindau's [18] disease or with the syndromes described by van Bogaert,[19] Zeldenrust,[20] Snapper and Formijne [21] and others. It must be included, however, in

the group of mesodermal or ectomesodermal dysplasias to which Recklinghausen's neurofibromatosis, Lindau's disease, the Sturge-Weber syndrome and, as recently reemphasized,[22] tuberous sclerosis probably belong. For the syndrome presented by our case we propose the term "progressive multiform angiosis."

SUMMARY

In the case reported the clinical picture was one of epileptic seizures, periodic disorderly behavior, dipsomaniac attacks and progressive mental deterioration. Autopsy revealed an arteriovenous angioma of the left parietal lobe, diffuse alterations of the subarachnoid vessels, a huge aneurysm of the circle of Willis and an aneurysm of the abdominal aorta. The subarachnoid vessels and the blood vessels of the angioma presented various stages of the "process of arteriolization" and other alterations. Calcification and brushlike proliferation were noted in cerebral capillaries.

In view of the observations in this case, we conclude:

1. No sharp distinction is possible between vascular malformations and vascular tumors of the brain.

2. Congenital defects may be a fundamental factor in the formation of cerebral and other aneurysms.

3. All the vascular lesions present in this case probably belong to but one pathologic entity.

On account of the difficulties of including the syndrome presented in this case in the modern classifications of the vascular disorders, the term "progressive multiform angiosis" is proposed.

16. Lévy, G.: L'angiomatose du système nerveux central, Presse méd. 38:37–40 (Jan. 8) 1930.

17. Panara, C.: Contributo alla conoscenza dell'angiomatosi cerebrale, Riv. di neurol. 7:579–606 (Oct.) 1934.

18. Lindau, A.: Studien ueber Kleinhirncysten: Bau, Pathogenese und Beziehungen zur Angiomatosis retinae, Acta path. et microbiol. Scandinav., 1926, supp. 1, p. 128.

19. van Bogaert, L.: Angiome caverneux du strié et malformations viscérales multiples, Rev. neurol. 71: 734–737 (June) 1939.

20. Zeldenrust, J.: Case of Angiomatoses cerebri, Am. J. Cancer 34:234–239 (Oct.) 1938.

21. Snapper, I., and Formijne, P.: Anevrysmen baseos cerebri en cysternieren, Nederl. tijdschr. v. geneesk. 82:5664–5669 (Nov. 26) 1938.

22. Ross, A. T., and Dickerson, W. W.: Tuberous Sclerosis, Arch. Neurol. & Psychiat. 50:233–257 (Sept.) 1943.

Obituaries

ROY DENNIS HALLORAN, M.D.
1894-1943

The death of Roy Halloran interrupted the development of a fine personality in the midst of its most productive period. He had recently been called to the post of chief of neuropsychiatry for the Medical Department of the United States Army, stationed in the Surgeon General's Office. His became the task of organizing and implementing with qualified personnel a branch of the Medical Department of the Army which has assumed a peculiarly critical importance during this war. No one could have shown better adaptability to the exigencies of emergent situations or more administrative competence or ability as team worker and team builder than did Roy Halloran. These qualities made him eminently suited to the task which had to be performed as a part of the immense and, perforce, cumbersome administrative machinery of an army in the process of building during a total war.

Colonel Halloran was born in Cambridge, Mass., Aug. 4, 1894. He received his degree of Bachelor of Arts from Dartmouth College in 1917 and his degree of Doctor of Medicine from Columbia University College of Physicians and Surgeons in 1920. While still a medical student he became interested in clinical and administrative psychiatric work. After serving his internship at the Newark City Hospital, he was assistant physician at the New Hampshire State Hospital and, later, at the Boston State Hospital, where he became assistant superintendent in 1928. It was here that, under the guidance of Dr. James V. May, then superintendent of the hospital, he developed as a psychiatrist and administrator. It was here, also, that, under the influence of Dr. Abraham Myerson, he became interested in teaching and investigative work. He collaborated with Dr. Myerson in the studies of cerebral metabolism and made with him a notable contribution in the development of the method of jugular venepuncture. This work became widely known in this country and abroad. He also published several papers on the administrative and social aspects of psychiatry.

In 1929 he became assistant to the commissioner of the Department of Mental Diseases of Massachusetts and in 1933 became first superintendent of the Metropolitan State Hospital.

During the nine years of his administration of this hospital, his abilities and personal qualities found their full expression. The conspicuous characteristic of his administrative methods was the courage with which he steered the development of the hospital along the line of research and teaching. He made it an educational community center for mental hygiene. He never hesitated to support and promote new ideas in the matter of utilization of hospital facilities for these purposes. He was always anxious to build and stimulate the spirit of professional dignity among members of the medical staff, and he made special efforts to induce them to have interests outside the narrow field of their routine daily activities. He detested gossip and mental stodginess, for the growth of which the closed institutions offer a propitious ground. He promoted investigative work at the hospital and prompted members of his medical staff to establish affiliations with other academic establishments and medical schools. He endeavored to offer the hospital facilities to these schools for lectures, clinical demonstrations and training of students and interns.

His inherent ability in building the spirit of teamwork about him was one of his great assets. To this, no doubt, he chiefly owed his accomplishments as administrator and organizer. This quality of his manifested itself in all phases of hospital activities. With Dr. Salomon Gagnon, then assistant superintendent, he was one of the first, if not the first, to establish a hospital library directed by a trained librarian, not merely as a diversional, but as a deliberately therapeutic, facility. The books were selected for the patients according to the therapeutic indications of their mental states. He promoted the department of occupational therapy, not merely as a routine to keep the patients out of mischief but as a means of providing an outlet for creative self expression. The exhibits of patients' paintings, sculptures, woodwork and carvings, held annually at the hospital, became in a sense a social event, with all the atmosphere of the *vernissage*. By these public exhibits, and by theatricals, shows and garden parties, he wished to bring the professional and the lay public to the hospital in order to break, as much as possible, the wall of

psychologic and social isolation of the patients in the hospital. This is generally done; yet his efforts in this direction were especially effective.

In 1936, under the impetus given by the establishment of the American Board of Neurology and Psychiatry, he founded postgraduate seminars in basic subjects pertaining to the specialty. Characteristically, he himself attended the lectures of the first seminar, with a small group of physicians who came from other psychiatric hospitals and from the community. Once he became convinced of the potential value of these seminars, he did not spare his efforts in promoting them and in providing all the necessary facilities for their development. Since the first one the seminars have been held annually, and nearly 400 graduate physicians from Massachusetts and neighboring states of New England have availed themselves of this educational facility. The Collected Lectures of the Seventh Seminar (1941-1942) on Military Neuropsychiatry, General Psychiatry and General Neurology, published under his direction by the Metropolitan State Hospital, found many appreciative readers among physicians, especially those in military service.

With such likable personal qualities and special abilities, it was not surprising when, in August 1942, he was called to Washington, D. C., to assume duties as chief of the neuropsychiatry branch of the Surgeon General's Office. He answered this call to a new and responsible position as a matter of duty to his country. To these duties he gave, as ever, all of himself. He died of coronary thrombosis on Nov. 10, 1943 and is buried at the Arlington National Cemetery.

PAUL I. YAKOVLEV, M.D.

Abstracts from Current Literature

Anatomy and Embryology

AGE INCIDENCE OF ATROPHY OF OLFACTORY NERVES IN MAN: A CONTRIBUTION TO THE STUDY OF THE PROCESS OF AGEING. CARLTON G. SMITH, J. Compt. Neurol. **77:** 589 (Dec.) 1942.

Smith examined 205 olfactory bulbs procured at autopsy from 121 persons of known age and sex who were free from intracranial disease. The ages ranged from birth to 91 years. By counting the number of olfactory glomeruli the author was able to estimate the number of fibers which reached a given bulb. The fibers began to disappear shortly after birth and continued to disappear at the rate of approximately 1 per cent a year. No sex difference in the loss of fibers was observed. Some subjects had entirely lost the olfactory fibers at the age of 20, and few had a normal count after the age of 50.

FRASER, Philadelphia

THE TROCHLEAR NERVE IN HUMAN FETUSES. ANTHONY A. PEARSON, J. Comp. Neurol. **78:** 29 (Feb.) 1943.

The nucleus of the trochlear nerve in older human embryos and fetuses is a large mass of multipolar neurons located just caudal to the nucleus of the oculomotor nerve. The division between the trochlear and the oculomotor nucleus is indicated by a thinning out of the cells of the motor column. The trochlear nucleus consists of a main mass of cells, with an occasional smaller mass which lies farther caudad. The caudal group of cells may be bilateral or unilateral. When unilateral it is present on either the right or the left side, with equal frequency. A few cells of the type found in the mesencephalic root of the fifth nerve occur in the main nucleus of the trochlear nerve. In some embryos scattered cells are observed along the course of the trochlear nerve central to its decussation. These cells resemble neuroblasts. The fibers of the trochlear nerve are collected into several small bundles along the dorsolateral border of the trochlear nucleus toward its caudal end. All trochlear fibers appear to decussate. The trigeminal nerve contributes a small bundle of fibers which course with the trochlear nerve along its peripheral path and become lost in the meninges.

ADDISON, Philadelphia.

LIPOFUSCIN DISTRIBUTION IN THE BASAL GANGLIA. RUDOLPH ALTSCHUL, J. Comp. Neurol. **78:** 45 (Feb.) 1943.

Altschul stained the basal ganglia of 2 children aged 3 months and 3 years respectively and of adults ranging in age from 42 to 84 years. He used a variety of stains to show the distribution of lipofuscin in nerve cells and neuroglia. The amount of lipofuscin in neuroglia cells of the basal ganglia was very small. The pigment was not a regular constituent of aging cells, but it occurred regularly in some of the cell systems. The nerve cells of the globus pallidus, the reticulate zone of the substantia nigra, the substantia innominata and the corpus subthalamicum were distinguished by the appearance and histochemical reaction of their lipofuscin. The nerve cells of the putamen and of the caudate and amygdaloid nuclei showed less typical reactions. Altschul believes that by the use of iron hematoxylin and basic fuchsin the lipofuscin present in the muscle of the human heart can be differentiated from the yellow pigment of nerve cells.

ADDISON, Philadelphia.

FUNCTIONAL RESULTS OF CROSSING SENSORY NERVES IN THE RAT. R. W. SPERRY, J. Comp. Neurol. **78:** 59 (Feb.) 1943.

In three stages Sperry crossed the nerves which mediate cutaneous and deep sensibility of the left hindfoot so that they innervated the right hindfoot. The first stage of the operation was performed on rats from 14 to 26 days of age. The second and third stages were delayed until the nerves previously crossed had regenerated. In a later series of operations the completely denervated left foot was amputated at the second stage. In a number of animals in which the nerves had been crossed, the left saphenous nerve was kept intact and about 1 cm. of the right saphenous nerve was excised. The animals were tested for signs of recovery by placing them on a platform with a floor of cloth, through which the plantar surface of

the foot could be stimulated. The first signs of recovery appeared about forty-eight days after the first operation. About sixty days after the left saphenous nerve had been crossed (stage 2) cutaneous sensitivity began to reappear on the dorsal surface of the foot. In all animals there were false localization of sensation and a decided maladaptive reversal of the reflexes of the hindlimb. Despite prolonged training under various conditions, the maladaptive spinal reflexes remained in every case wholly uncorrected, or even inhibited by adjustment in the central nervous system.

ADDISON, Philadelphia.

THE DEVELOPMENTAL CONTROL OF PARS INTERMEDIA BY BRAIN. WILLIAM ETKIN, J. Exper. Zool. 92:31 (Feb.) 1943.

In embryos of Rana pipiens, pituitary primordia, with and without varying amounts of neighboring brain tissue, were transplanted into young hypophysectomized animals. It was found that primordia developing in isolation from brain tissue induce excessive pigmentation in the host and show histologic evidence of overgrowth and hyperactivity. Primordia developing in contact with brain tissue at regions other than the infundibular floor behave as do isolated primordia. On the other hand, primordia developing in contact with the floor of the graft infundibulum at or near the normal point of attachment develop normally and show no evidence of excess function or growth. In grafts of the last type diencephalon with varying amounts of adjacent tissue was present. Grafts that do not take successfully may induce approximately normal pigmentation in the host.

These results seem to support the previously developed thesis that control of activity and growth of the pars intermedia is normally effected by inhibitory impulses brought to the gland over the hypothalamohypophysial nerve tracts. The effectiveness of control by an isolated section of brain indicates that the mechanism is not purely reflexive.

REID, Boston.

EXPERIMENTAL STUDIES ON THE DEVELOPMENT OF THE CORNEAL REFLEX IN AMPHIBIA: III. THE INFLUENCE OF THE PERIPHERY UPON THE REFLEX CENTER. JERRY J. KOLLROS, J. Exper. Zool. 92:121 (March) 1943.

In Amblystoma (several species) and Triturus torosus the presence of a supernumerary eye in the otic area of the head modifies the response elicitable from that area. Stimulation of the extra cornea results in a retraction of the host eye on the same side instead of a head flexure (Triturus).

In Triturus, Amblystoma and Rana pipiens there is an increase in the sensitivity to tactile stimuli of the skin lying between the host and the graft eyes. In Triturus, and probably in Amblystoma, the influence of the graft is exerted throughout the larval period and beyond metamorphosis. The shrinkage of the reflexogenous area after metamorphosis (Triturus) is prevented, and there is an increase in local sensitivity. In Amblystoma and Rana the sensitivity of the graft also increases after metamorphosis.

Reduction in extent of the host cornea fails to reduce the extent of the reflexogenous area. Only the area of the replaced cornea itself has a lower sensitivity.

The cornea need not be completely differentiated to permit modulation of the sensory nerve fibers entering it.

REID, Boston.

Physiology and Biochemistry

EXPERIMENTAL RIBOFLAVIN DEFICIENCY IN MAN. JOHN J. BOEHRER, CHARLES E. STANFORD and ELIZABETH RYAN, Am. J. M. Sc. 205: 544 (April) 1943.

The authors chose 6 volunteers, 1 man and 5 women, who previously had had dietary treatment for obesity. The subjects were divided into two groups of 3 each, designated as the "control" and the "experimental" group. The experimental, low riboflavin diet contained 471 mg. of riboflavin. All 6 patients received a daily supplement of vitamins and minerals, and the controls received, without their knowledge, a daily supplement of 3 mg. of riboflavin. The experiment was terminated after only five weeks of observation because of external circumstances. Each volunteer reported for study with the slit lamp. The failure of corneal vascularization to develop was not in accordance with the reported observations of Sydenstricker, Kelly and Weaver. It was significant that definite evidence of corneal vascularization occurred in 1 of the subjects of the control group, in spite of an intake of riboflavin of approximately 3.5 mg. per day, whereas an intake of approximately 2.1 mg. of riboflavin per day for seventy-nine days previously, while the subject was on the reduction diet, had not resulted in keratitis.

MICHAELS, Martinsburg, W. Va.

THE EFFECT OF SECTIONING VARIOUS AUTONOMIC NERVES UPON THE RATE OF EMPTYING OF THE BILIARY TRACT IN THE CAT. FRANK E. JOHNSON and EWARD A. BOYDEN, Surg., Gynec. & Obst. **76**:395, 1943.

The specific pathways to the choledochoduodenal junction, namely, the gastroduodenal nerve and plexus, were interrupted in cats. In one group of animals only the plexus was sectioned; in these cats the rate of emptying of the gallbladder following the ingestion of food appeared normal. But when the gastroduodenal nerve was cut in addition to the fibers of the plexus, decided retardation in the rate of emptying was observed. These observations were believed to indicate that the gastroduodenal nerve carries fibers which lower the resistance at the biliary outlet. Therefore the severance of nerves to the choledochoduodenal junction in patients should not be expected to lower the resistance to the flow of bile, but rather should increase it. The severance of the gastroduodenal nerve or plexus or both failed to affect or to abolish the inhibitory reflex to the gallbladder on electrical stimulation of the cecum. This result, therefore, appears to prove that stoppage of flow of bile from the gallbladder, as a result of visceral pain, is not dependent on action of the sphincter, since the tonus of the gallbladder can be inhibited in the absence of nerves to the choledochoduodenal junction.

Section of the right vagus nerve, which gives the only vagal component to the gastroduodenal nerve, resulted not only in increased resistance to the flow of bile at the sphincter but in decreased contractile force applied by the gallbladder, for the rate of emptying was much slower when the right vagus nerve was cut than when only the gastroduodenal nerve was eliminated. Section of the left vagus nerve also retarded the emptying of the gallbladder, but to a lesser degree than did section of the right vagus nerve.

Severance of the splanchnic roots of the celiac ganglia as far down as the second lumbar nerve abolished the inhibitory reflex from cecum to gallbladder and resulted in a somewhat accelerated rate of emptying of the gallbladder. Since section of the nerve to the sphincter (gastroduodenal nerve) retarded the flow of bile, the inference is that this nerve does not carry sympathetic inhibitory fibers. The retardation obtained by section of the vagus nerves was much greater than the acceleration caused by section of the splanchnic fibers.

When both the major and the minor splanchnic nerves were cut but the least splanchnic nerve was spared, the inhibitory reflex to the gallbladder was abolished, but the perception of pain on electric stimulation of the cecum persisted. This implies that pain impulses from the cecum enter the spinal cord as low as the second lumbar sympathetic ganglion, having traversed the superior mesenteric plexus and the least splanchnic nerve.   SHENKIN, Philadelphia.

DISCHARGES FROM VESTIBULAR RECEPTORS IN THE CAT. E. D. ADRIAN, J. Physiol. **101**:389, 1943.

Nerve impulses from vestibular receptors were studied in the cat by means of oscillographic records obtained by insertion of fine wire electrodes into the brain stem in the region of the vestibular nuclei. Two main types of discharges from single units were observed, one controlled by gravity and the other by rotation. The former were found to depend on the position of the head in space; the latter, only on angular accelerations or decelerations. Discharges controlled by horizontal rotation and by the tilt of the head in the median plane were found near the oral border of the striae acusticae. Those controlled by lateral tilt and by rotation in the transverse plane were near the aboral border. Responses to vibration, such as have been reported in frogs, were not observed in cats.

The gravity receptors were increasingly stimulated as the head was tilted out of its normal position and became slowly adapted to the stimulus. They reacted to linear accelerations, as well as to the pull of gravity.

The rotation receptors were stimulated by angular acceleration in the horizontal, median or transverse plane or by deceleration of steady rotation in the nonstimulating sense.

The quick turns of the head were signaled by brief discharges which coincided with the movement, but acceleration not followed at once by deceleration gave discharges lasting up to twenty-five seconds. Equally long after-discharges followed deceleration from steady rotation in the nonstimulating sense.

The majority, but not all, of the rotation receptors gave persistent low frequency discharges when the head was at rest. These were suppressed by acceleration in the nonstimulating sense. The results support the view advanced by Ross that the receptors of the canals adapt slowly, the stimulus being proportional to the deflexion of the cupola. With a brief turn the reversal of the endolymph flow brings the cupola back at once to the mid-

position; with continued rotation the deflected cupola is brought back slowly by elastic forces and is then deflected in the other direction when rotation is stopped.

THOMAS, Philadelphia.

THE NEUROPHYSIOLOGY OF THE PARKINSON TREMOR. M. W. THORNER, Confinia neurol. 5:113, 1942.

Thorner investigated the tremor of Parkinson's disease by means of electromyography. He expresses the belief that the tremor is a complicated form of oscillatory activity involving neural, muscular and mechanical components, which occurs as a result of the release of the normal damping effect of the basal ganglia. There is reciprocal and alternating contraction of antagonistic muscles. The frequency of the oscillation decreases as friction of the oscillating system increases and as the mass of the tremulous part is increased. A "feed back" mechanism is required for maintenance of the amplitude of the tremor. This is contained in part in the afferent return from the muscles involved and in part in the motor pathways of the central nervous system.

DEJONG, Ann Arbor, Mich.

MOVEMENTS OF LOCOMOTION IN THE DECEREBRATE CAT. CARLOS GUTIÉRREZ-NORIEGA, Rev. de neuro-psiquiat. 4:333 (Sept.) 1941.

This is a physiologic study of locomotion by a pharmacologic method whereby all motor areas can be stimulated simultaneously with equal intensity. If locomotion were controlled from a limited area, the electrical method would be superior to the pharmacologic method, but since it is more probable that locomotion is an integrated action of many centers of the neuraxis, the pharmacologic method is preferable.

The procedure for study consisted of decerebration of the animal at the desired level, sufficient time being allowed for recovery from the effect of trauma; careful examination was made of all reactions of the animal (reflexes, tone, and movements of deambulation, spontaneous or provoked by electrical or mechanical stimulation); finally, nikethamide was injected into the saphenous vein, and the intensity and duration of the reaction were noted.

The following types of decerebrate cats were studied: bulbar, in which the transverse section was between the protuberance and the pons Varolii; hemiprotuberance, with the transverse section at the midpoint of the protuberance; protuberance, with the transverse section between the mesencephalon and the protuberance; hemimesencephalic, with the section in a transverse plane passing between the superior and inferior corpora quadrigemina posteriorly and the middle of the cerebral peduncules anteriorly; mesencephalic, with the plane of section from the superior border of the superior quadrigeminal bodies to the superior part of the mamillary bodies, and, finally, thalamic.

The term deambulation is used to indicate a complete function which permits each animal to displace itself in space and is integrated at least by the following elemental movements: rhythmic movements of flexion and extension of the extremities, which may also be called movements of progression or of deambulation; postural tone, in this case the tone of progression, and equilibrium. Only the movements of deambulation, which need not be confused with deambulation in general, are discussed.

Nikethamide was found to be the best stimulus in producing movements of deambulation. A specific center for locomotor function could not be isolated, for in the cat and dog an extensive region from the basal ganglia to the bulb takes part in this function. With the technic of progressive removal of the neuraxis, it was found that the magnitude of the disturbance of locomotor function produced by a lesion was directly related to the quantity of neural tissue removed, especially tissue from the cerebral trunk and basal nuclei.

Combined surgical-pharmacologic study disclosed that thalamic and diencephalic animals retained an almost normal gait. In mesencephalic animals deambulation was imperfect, since they walked with the legs semiflexed and fell at the slightest obstacle. The hemimesencephalic animals lost the capacity to deambulate, but if stimulated with nikethamide they presented powerful movements of flexion and extension of the forelimbs similar to those of running. The protuberance animals had poorer and less lasting responses than hemimesencephalic preparations when stimulated with nikethamide or metrazol, but the movements were more vigorous and there was more definite participation of all four limbs than in the hemiprotuberance animals. The latter had weaker and less lasting movement, mainly of the forelimbs, and required a larger dose of the drugs for effect. The bulbar animals failed to produce rhythmic movements of deambulation in the forelimbs, but in rare instances weak alternate movements of flexion and extension could be obtained in one limb or in a pair of limbs.

Thus, the various factors which integrate deambulation disappear in a progressive manner according to the amount of destruction of cerebral trunk, from the basal nuclei to the bulb. Extirpation of the cerebellum failed to modify the effect of nikethamide on the movements of deambulation.

Gutiérrez-Noriega demonstrated that the zone between the basal ganglia and a plane which passes between the bulb and the protuberance is particularly concerned with movements of deambulation in the cat. Although it is certain that deambulation, strictly speaking, is found only in thalamic and diencephalic animals, the simple movements of deambulation of the extremities can originate from electrical, mechanical or pharmacologic stimuli to inferior parts of the neuraxis. Such movements can be obtained in animals in which only the inferior part of the protuberance is preserved. From this the author concludes that movements of deambulation cannot be localized in a specific center or in a limited group of centers. Even less so can locomotion be localized. It is certain that the efficiency of the act of progression diminishes proportionately with the amount of neural tissue removed.

The thalamic animal walks, but not as perfectly as the intact animal. If the thalamus is removed the stability, frequency and complexity of movements diminish. The mesencephalic animal walks defectively or, better, drags itself about with the legs semiflexed, but if it is put in dorsal decubitus it can move the four extremities perfectly with the same series of combinations of flexion and extension of the four limbs as is required in normal progression. Therefore, extirpation of the thalamus, including the hypothalamus, affects principally not the rhythmic movements of the extremities but the distribution of tone and of equilibrium necessary to maintain the animal erect during deambulation.

DE GUTIÉRREZ-MAHONEY, Coral Gables, Fla.

EXPERIMENTAL CATALEPSY PRODUCED BY NICOTINE. CARLOS GUTIERREZ-NORIEGA, Rev. de neuro-psiquiat. 5:323, 1942.

Gutierrez-Noriega studied the cataleptic action of nicotine in dogs. One hundred animals were divided into five groups of 20 each, each group receiving a different dose of nicotine tartrate, varying from 1 to 5 mg. per kilogram of body weight. The drug was injected into the saphenous vein in a 1 per cent solution. The intensity of the cataleptic state was measured by the duration of abnormal postures. Three observations were made: (1) the average frequency of occurrence of the cataleptic state in each group; (2) the average intensity, and (3) the average duration. From the data he obtained a "cataleptic index"—one-tenth the sum of the three values. Observations were also made on the severity of the convulsions and their relation to the intensity of the catalepsy. The results obtained indicated that nicotine tartrate can cause reactions of cataleptic type, as well as other manifestations of experimental catatonia, such as motor excitation, neurovegetative changes and lack of response to painful stimuli. The doses that produce these reactions are also convulsant, but the catalepsy may appear independently of convulsions. In fact, the optimum dose for production of catalepsy (3 mg. per kilogram) is not the optimum dose for production of convulsions.

Although there is a correlation between the dose and the intensity of the cataleptic reaction, there is a still greater relation to the constitution of the animal, docile, quiet and friendly animals being more susceptible than active, impetuous and surly dogs. The author suggests that his method of obtaining a cataleptic index be used in study of the action of drugs of this type in large numbers of animals. Several graphs and charts illustrate the paper.

Meninges and Blood Vessels

HEMIPLEGIA IN TUBERCULOUS MENINGITIS. CLARENCE W. OLSEN and ALBERT F. BROWN, Bull. Los Angeles Neurol. Soc. 7:189 (Dec.) 1942.

Olsen and Brown report 4 cases of hemiplegia associated with tuberculous meningitis. The incidence of this complication in a series of 378 cases of tuberculous meningitis with both clinical and postmortem reports slightly exceeded 10 per cent. LESKO, Bridgeport, Conn.

RESPONSE OF PFEIFFER'S BACILLUS MENINGITIS TO SULPHAPYRIDINE. RAYMOND A. MOIR, Lancet 1:556 (May 1) 1943.

Moir reports 4 cases of meningitis due to Haemophilus influenzae. In only 2 of these 4 cases did recovery occur. He believes that the bacilli were too scanty in the original smear of the cerebrospinal fluid for much credit to be attributed to the drug for the recovery in 1 of the 2 cases. Fothergill and Sweet (J. Pediat. 2:696, 1933) reported only 1 spontaneous recovery in 78 cases. The other recovery in Moir's cases (that of a 10 month infant) he feels was a true cure, especially since children under 1 year of age have not been known to recover spontaneously.

In this series Moir noted that the temperature might drop to normal only to rise again, whereas the pulse stayed high until the temperature had fallen permanently. Hence the pulse is taken as a more reliable guide in prognosis than the temperature.

He recommends that lumbar puncture be done once for diagnosis, the procedure to be repeated only if restlessness and irritability become uncontrollable; otherwise, a second tap should not be done until the patient is clinically well.

Administration of sulfapyridine in doses of no less than 3 Gm. per twenty-four hours is advised with continuation of the drug in reduced doses for two weeks after meningitic signs are gone.   McCARTER, Philadelphia.

PNEUMOCOCCAL MENINGITIS: RECOVERY AFTER SULPHAPYRIDINE AND SERUM THERAPY. H. A. THOMAS, R. J. TWORT and C. P. WARREN, Lancet **1**:581 (May 8) 1943.

The authors report a case of pneumococcic meningitis following mastoiditis. The patient was first treated with sulfapyridine but in a few days was also given type-specific antipneumococcic serum, since he was not improving under treatment with the drug alone. There was rapid change for the better after the first 100,000 units (U. S. P.) of the serum, a change so dramatic that the authors suggest it was more than coincidence and probably indicates that the serum was the chief curative factor. Several days after convalescence had begun sciatic neuritis with foot drop developed on the right side. Intramuscular injection of the sulfapyridine is offered as the most likely cause of this complication. In the sixth month after the illness developed the patient suddenly had a focal epileptic attack, followed by hemiparesis and motor aphasia, from which he slowly recovered.

McCARTER, Philadelphia.

THE RELATIONSHIP BETWEEN BENIGN LYMPHOCYTIC MENINGITIS AND POLIOMYELITIS. P. GAUTIER and G. HENNY, Confinia neurol. **4**:309, 1942.

Gautier and Henny note certain similarities between lymphocytic choriomeningitis and poliomyelitis, namely, in the constituents of the spinal fluid, in the epidemiology and in the clinical course. They state that the two conditions often occur simultaneously. They express the belief that all cases of lymphocytic meningitis which run a benign course should be regarded as instances of an attenuated form of poliomyelitis or of poliomyelitis in which the disease process is limited to the meninges.   DeJONG, Ann Arbor, Mich.

THROMBOSIS OF THE COMMON CAROTID ARTERY. T. FRACASSI, Semana méd. **49**:1004 (May 14) 1942.

Fracassi reports a case in which a clinical diagnosis of thrombosis of the common carotid artery with complete occlusion was made. No clinical diagnosis of this condition has previously been reported in the literature. In the case reported by Wohlwill, necropsy revealed syphilitic aortitis with thrombosis of the common carotid artery at the point of its origin. The communicating posterior artery of the opposite side was so greatly dilated that an adequate collateral circulation had been established to take care of the occluded side. Fracassi's patient, aged 58, had a chancre in his youth. The chancre disappeared without treatment. The patient at no time exhibited syphilitic, circulatory or nervous symptoms. At the examination it was found that he had suffered for about three months from intermittent attacks of local pallor and coldness of the right hand and foot. There was also an attack of apoplexy, with coma of ten hours' duration, transient aphasia and right hemiplegia. The patient complained of pulsation and pain in the region of the right temporal artery and its branches, which did not yield to analgesics. The heart was normal. The pulse was normal, with a maximum arterial pressure of 100 mm. The Wassermann reaction was positive. Bismuth and mercury therapy was administered. Three years later the patient was in a satisfactory state of health, with normal intelligence and normal speech. An aortic murmur was audible. The roentgenographic shadow of the aorta was widened. Electrocardiograms showed changes in the myocardium. The left common carotid artery and its internal and external branches and the left temporal, angular and facial arteries did not pulsate. The right common carotid artery and its branches pulsated strongly. The blood pressure in the right radial artery was 115 mm., while in the left it was 100 mm. The retinal vessels of the left eye were narrowed. There was normal pulsation in both pedal arteries. Right hemiplegia and deep and superficial anesthesia were present on the right side. A clinical diagnosis of thrombosis of the common carotid artery was made. The hemiplegia was caused by softening of the brain tissue in the region of the left sylvian artery. The dilatation and forced pulsation

of the right local arteries, on the one hand, and the narrowing of the left retinal vessels, on the other, confirmed the diagnosis. The author emphasizes the diagnostic significance of the absence of pulsation in the temporal and carotid arteries of one side and of forceful pulsation of the arteries of the opposite side in cases of hemiplegia, changes which indicate thrombosis of the primary common carotid artery.

<div align="right">J. A. M. A.</div>

CHRONIC TUBERCULOUS CEREBROSPINAL LEPTOMENINGITIS. B. SCHMIDT, Beitr. z. Klin. d. Tuberk. **96**:124 (March 21) 1941.

Schmidt reports the case of a man, aged 28 who, since the age of 18, had presented obscure cerebral symptoms with convulsions, loss of consciousness and mental disturbances. Necropsy disclosed chronic tuberculous cerebrospinal leptomeningitis with tubercles in the dura, internal hemorrhagic pachymeningitis, calcified foci in the tracheobronchial lymph nodes, inflammatory swelling and tuberculosis of the paratracheal and hilar lymph nodes of both lungs, pleural adhesions and catarrhal urocystitis with dilatation of the bladder, ureters and renal pelves. Microscopic examination of the lymph nodes disclosed calcified tuberculous foci. The microscopic aspects of the brain are described in detail. There was evidence that the chronic tuberculosis of the leptomeninges had a *strong tendency to cicatrization*. The author cites 3 similar cases from the literature.

<div align="right">J. A. M. A.</div>

MENINGOCOCCIC MENINGITIS TREATED WITH SULFATHIAZOLE. H. PEDERSEN and J. WILKEN-SCHILDT, Ugesk. f. læger **103**:1562 (Dec. 4) 1941.

Because of its easier absorption and elimination and its less toxic by-effects, Pedersen and Wilkenschildt consider sulfathiazole superior to the other sulfonamide compounds previously used in the treatment of meningococcic meningitis. They report 11 cases in which this agent was employed, in 7 of which the condition was toxic, with cutaneous metastases. In all the cases meningococci were present in the spinal fluid. Nine of the patients recovered rapidly; 2 died, 1 a child aged 5 months and the other a man who was moribund on admission. The sulfathiazole was administered orally in tablet form except in the case of the 5 month old child, to whom it was given intramuscularly.

<div align="right">J. A. M. A.</div>

Diseases of the Spinal Cord

ENCEPHALO-MYELO-RADICULITIS. CHARLES G. POLAN and A. B. BAKER, J. Nerv. & Ment. Dis. **96**:508 (Nov.) 1942

Polan and Baker report 8 cases of encephalomyeloradiculitis, calling attention to the diversity of terms under which the disease has been described. They regard the condition as a syndrome. In most cases the disease is preceded by an infection of the upper respiratory tract. Neurologic symptoms are sudden in onset and consist of muscular weakness or paralysis, distal hyperesthesias, radicular pain and aching muscles. The lower extremities, especially the distal parts, are more often involved early in the disease. Unilateral or bilateral weakness of the face is common. Objective signs are variable, but usually appear as ascending flaccid paresis or paralysis with diminished deep reflexes. Sensory disturbances follow a segmental or radicular distribution. The temperature and leukocyte counts are usually normal, or only slightly elevated. A high protein content of the spinal fluid with a normal cell count is characteristic of the disease, but it is not constant. Most patients begin to recover after an acute onset, but recovery is usually slow. Fatalities are infrequent and are usually due to complications or involvement of the medulla. Treatment is symptomatic and includes rest in bed, use of the Drinker respirator when necessary, small transfusions, administration of large doses of vitamins B and C, tidal irrigations of the bladder, administration of sulfonamide compounds in cases of involvement of the bladder and physical therapy for muscle disorders. Pathologic lesions vary with the extent and location of the disease process. In 1 case there were fairly extensive injury to the neurons of the cranial nerves and spinal cord and scattered areas ot focal demyelination involving the gray and the white matter, most of it scattered around the blood vessels.

<div align="right">CHODOFF, Langley Field, Va.</div>

TONSILLECTOMY AND POLIOMYELITIS. J. A. TOOMEY and C. E. KRILL, Ohio State M. J. **38**:653 (July) 1942.

Toomey and Krill tabulate the results of fourteen years' experience in the relation of poliomyelitis to tonsillectomy at the Children's Hospital in Akron, Ohio, and of one year's experience at the City Hospital of Cleveland. Seventeen of the 210 patients at the Children's

Hospital died, as did 18 of the 220 patients at the City Hospital. In 14, or 82 per cent, of 17 patients who had had a tonsillectomy or adenoidectomy within thirty days prior to the onset of poliomyelitis the bulbar type of paralysis developed. Of 134 patients operated on prior to thirty days before onset at both hospitals, 52 had bulbar poliomyelitis. Eight, or 50 per cent, of the 16 children with the bulbar type died. At the City Hospital 8 of the 36 died. In 7, or 5 per cent, of 140 nonsurgical patients admitted to the Children's Hospital and 23, or 19.4 per cent, of 118 similar patients admitted to the City Hospital bulbar poliomyelitis developed. Here, again, most of the children who died had the bulbar type—5 of the total 7 at the Children's Hospital and the 9 at the City Hospital. If only the mortality of the group that had spinal or nonparalytic poliomyelitis is considered, the rate seems insignificant —2 per cent at the Children's Hospital and none at the City Hospital. The many persons who had had tonsillectomy and adenoidectomy within thirty days of the development of bulbar poliomyelitis cannot be explained on the basis of mere chance or random sampling. In the regions discussed, it appears to be advisable to do tonsillectomies in the late spring.

J. A. M. A.

Cerebrospinal Fluid

THE CEREBROSPINAL FLUID. ROQUE GRAZIANO, Rev. argent. de neurol. y psiquiat. **7**:83 (June) 1942.

On the basis of a review of the anatomic relation, chemical composition, circulation, cytologic characteristics and diagnostic significance of the cerebrospinal fluid, Graziano concludes: 1. Studies of the cerebrospinal spaces at autopsy confirm the concept that the cerebrospinal fluid is formed by the choroid plexuses. 2. The cerebrospinal fluid varies in composition in different regions of the cerebrospinal spaces. 3. Analysis of the cerebrospinal fluid at various stages of the course of a disease enables one to determine the development of the malady, just as do the clinical symptoms. This is illustrated by the evolution in the number of lymphocytes and polymorphonuclear leukocytes in the course of pneumococcic meningitis. 4. The constellation of findings in the fluid, not its separate constituents, is important for diagnosis. 5. In diseases of the nervous system caused by Treponema pallidum the constellation of findings in the fluid differs from that in other diseases.

BAILEY, Chicago.

Treatment, Neurosurgery

NON-CONVULSIVE ELECTRIC (FARADIC) SHOCK THERAPY OF PSYCHOSES ASSOCIATED WITH ALCOHOLISM, DRUG INTOXICATION AND SYPHILIS. NATHANIEL J. BERKWITZ, Am. J. Psychiat. **99**: 364 (Nov.) 1942.

Berkwitz reports the results of nonconvulsive electric shock treatment of 67 patients with alcohol and drug addiction and of 5 patients with dementia paralytica. This treatment was given in addition to the generally accepted therapeutic regimens. Most patients showed improvement with one to four treatments; only rarely was it necessary to administer more than ten shocks. Improvement manifested itself chiefly by decrease in the period of delirium.

FORSTER, Philadelphia.

SUBCONVULSIVE ELECTRIC SHOCK TREATMENT OF THE PSYCHOSES. WALTER A. THOMPSON, Am. J. Psychiat. **99**: 382 (Nov.) 1942.

Thompson reports on the use of subconvulsive electric shock therapy with 213 patients. The shocks were induced by a faradic current of high voltage and low amperage passed between the head and the leg electrode. The result was a tetanus-like convulsion without loss of consciousness. No particular group of patients was studied, the conditions of the patients representing all types of psychoses available. No cures were obtained, but 65 per cent of the series showed some improvement in hospital adjustment.

FORSTER, Philadelphia.

THE TREATMENT OF PSYCHOSES WITH LONG PROTRACTED INSULIN COMA. JOSEPH WORTIS, MILTON TERRIS and IRVIN M. KORR, Am. J. Psychiat. **99**: 391 (Nov.) 1942.

Wortis, Terris and Korr have succeeded in prolonging hypoglycemia for twenty-four hours and coma for twenty hours by maintaining the blood sugar at a moderately high level (35 mg. per hundred cubic centimeters). Irreversible coma could be prevented by careful attention to the blood sugar level, the pulse rate, the temperature and the patient's general condition.

Caution in the general application of this form of therapy is recommended. The authors have no adequate statistics on the therapeutic value of this treatment but indicate that it may be more advantageous than the usual insulin therapy.

FORSTER, Philadelphia.

EVALUATION OF THE EFFECTS OF INTRAVENOUS INSULIN TECHNIQUE IN THE TREATMENT OF MENTAL DISEASES. PHILLIP POLATIN and HYMAN SPOTNITZ, Am. J. Psychiat. **99**:394 (Nov.) 1942.

Polatin and Spotnitz report the results of insulin shock therapy induced by intravenous administration of insulin or protamine zinc insulin crystals. The protamine zinc insulin preparation was used when patients were allergic to unmodified insulin. The authors treated 33 patients, 24 of whom were schizophrenic. Definite improvement occurred in 14 patients, 4 of whom had a relapse within two years. The authors believe that the intravenous administration of insulin for induction of shock is the method of choice for patients with psychoses of acute onset and short duration.

FORSTER, Philadelphia.

PREFRONTAL LOBOTOMY IN CHRONIC PSYCHOSES. MAGNUS C. PETERSEN and HAROLD F. BUCHSTEIN, Am. J. Psychiat. **99**: 426 (Nov.) 1942.

Petersen and Buchstein studied 46 patients who had undergone prefrontal lobotomy for long-standing psychoses. Psychic tension was the criterion for operation. No patient died as a direct result of the operation, but 1 patient died eleven days after operation of pharyngeal obstruction due to her failure to swallow food. The importance of this situation is stressed. Flushing and sweating occurred immediately after the section of cerebral tissue, and in some instances conjugate ocular deviation and a positive Babinski sign were noted. Bradycardia and hypotension occurred constantly, the bradycardia being of longer duration than the hypotension. Most of the patients had increased appetite after the operation, and 13 showed increased dextrose tolerance. Almost all the patients manifested untidiness. The most striking phenomenon was relief from tension immediately on bilateral section. Sixteen of the authors' 29 patients who were operated on in 1941 showed improvement.   FORSTER, Philadelphia.

ELECTRIC SHOCK TREATMENT IN GENERAL PARESIS. GERT HEILBRUNN and PAUL FELDMAN, Am. J. Psychiat. **99**:702 (March) 1943.

Heilbrunn and Feldman administered from two to seven electric shock treatments to each of 5 patients with dementia paralytica. No improvement in the clinical condition was noted. However, therapy had to be discontinued because of the development of alarming cardiovascular and respiratory complications. These were attributed to the heightened vulnerability of the ganglion cells in neurosyphilis. Heilbrunn and Feldman conclude that electric shock therapy is a perilous therapeutic procedure for dementia paralytica.

FORSTER, Philadelphia.

ON THE USE OF STRYCHNINE IN THE CURARE-AIDED METRAZOL TREATMENT OF PSYCHOSES. MARCEL HEIMAN, Am. J. Psychiat. **99**:706 (March) 1943.

Heiman administered simultaneously strychnine and curare to 30 female patients with psychoses and followed this with metrazol. He found that strychnine reduced the metrazol requirement and had a beneficial influence on respiration, its action thus tending to offset the central effect of metrazol and the peripheral effect of curare.   FORSTER, Philadelphia.

EXTRA-MURAL SHOCK THERAPY. LOUIS WENDER, BENJAMIN H. BALSER and DAVID BERES, Am. J. Psychiat. **99**: 712 (March) 1943.

Wender, Balser and Beres treated with electric shock 40 patients from the office and outpatient department, 31 of whom had major psychoses. The authors consider the patient's refusal to be hospitalized or the physician's opinion that it is not advisable as indications for extramural therapy. The technic differed in no way from the intramural method. The average duration of therapy was five weeks. There were 6 failures in the entire series. The authors conclude that the results are comparable to those obtained with hospitalized patients. The importance of follow-up psychotherapy is stressed.   FORSTER, Philadelphia.

Vitamin B Therapy in Paralysis Agitans. Winifred C. Loughlin, H. Arnold Myersburg and Herman Wortis, Ann. Int. Med. **17:** 423 (Sept.) 1942.

Twenty-two unselected patients with paralysis agitans were used as subjects in a determination of the effects of vitamin B therapy. The ages ranged from 28 to 72 years, the average age being 49.2 years. The duration of symptoms varied from three to thirty-three years. The patients were divided into two groups; a group of 12 patients received daily intravenous doses of vitamins, while the other group, of 10 patients, received daily injections of 5 cc. of isotonic solution of sodium chloride. All the patients continued to have whatever other therapy they were receiving prior to the onset of the experiment. Examinations were made at weekly intervals during the experiment. The vitamin-treated patients received intravenous injections of a preparation containing 10 mg. of thiamine hydrochloride, 10 mg. of nicotinamide, 1 mg. of riboflavin, 10 mg. of pyridoxine hydrochloride and a buffered solvent up to 5 cc. Each patient received six intravenous injections each week for five and one-half weeks, and for the next five weeks the same number of injections weekly, with the addition of 90 mg. of pyridoxine hydrochloride. The controls received daily injections of 5 cc. of sterile isotonic solution of sodium chloride for ten and one-half weeks.

There was no objective improvement in the vitamin-treated group. Two patients in the group reported subjective improvement. Of the control group, 9 showed initial subjective improvement, in 3 of whom it persisted throughout the treatment. One of the patients, of the control group, showed objective improvement. Price, Philadelphia.

The Treatment of Essential Hypertension by Sympathectomy. James Bordley III, Morton Gladston and Walter E. Dandy, Bull. Johns Hopkins Hosp. **72:** 127 (March) 1943.

The presence of incapacitating symptoms was the only criterion for sympathectomy in 12 patients with essential hypertension. Ten of the patients were from 28 to 40 years and 2 were 50 years of age at the time of operation. In 3 patients a supradiaphragmatic splanchnicectomy (Peet operation), and in 9 patients an infradiaphragmatic splanchnicectomy (Adson-Craig operation), was performed. The level of the arterial pressure was lower for six to eighteen months in 4 of the 9 patients treated by infradiaphragmatic operation. Symptomatic relief, obtained in 4 patients, seemed to depend on lowered arterial pressure. In 2 patients on whom the infradiaphragmatic (Adson-Craig) operation was performed the abnormal signs referable to the heart and eyegrounds regressed during the period of lowered arterial pressure but returned with elevation of the pressure. The return of the arterial pressure to hypertensive levels was not accompanied by regeneration of the sympathetic nerves to the lower extremities after the Adson-Craig operation. The group of patients was not large enough to warrant the formation of conclusions concerning the relative incidence of reduction in the level of arterial pressure following sympathectomy in patients with changes in the eyegrounds, of various degrees of severity. Price, Philadelphia.

Society Transactions

CHICAGO NEUROLOGICAL SOCIETY

ARTHUR WEIL, M.D., *President, in the Chair*

Regular Meeting, April 15, 1943

Plastic Repair of Defects of the Skull. DR. HAROLD C. VORIS.

Materials available for the repair of defects of the skull may be divided into three general groups: living autogenous bone or cartilage; boiled or preserved bone or cartilage, and alloplastic materials, of which pyroxylin and various metals have been the most popular. Living bone or cartilage may be obtained from various parts of the patient's body, but the two most common sources are the ribs or costal cartilages and the periosteum and attached fragments of the outer table of the skull. Rib or portions of the skull can be obtained from other persons or from cadavers and can be sterilized by boiling before insertion. The greatest use, however, for such grafts is the replacement of areas of skull invaded by tumor cells, after such areas have been temporarily removed and boiled.

Pyroxylin has been widely used in the past, as well as many metals, particularly silver, gold and aluminum. The recent investigations of Venable, Campbell, Pudenz and others have shown that certain alloys and metals are noncytotoxic; of these, vitallium, tantalum and ticonium (wrought) appear to be the best.

Cases are presented, with lantern slides from these and other cases, illustrating the replacement of bone flaps after boiling, plastic repair with rib or rib cartilage, employment of grafts consisting of periosteum and the outer table of the skull and, finally, use of the vitallium plate.

Repair of defects of the skull is indicated (1) for cosmetic reasons; (2) for protection, when the occupation renders the patient particularly liable to head trauma; (3) for severe subjective symptoms, such as headache, dizziness and pain in the region of the defect; (4) for undue pulsation of the scalp overlying the defect; (5) for economic reasons, when the patient is unable to obtain a position because of the presence of a defect in the skull, and (6) for relief of an unfavorable psychic effect. All defects of the frontal region below the hair line, including those of the supraorbital ridge, should be repaired. Small defects within the hair line seldom need repair; large defects within the hair line which fall into one of the classes just indicated may be repaired. A graft consisting of periosteum and attached fragments of the outer table of the skull is the most satisfactory for small defects. The use of rib or costal cartilage is advised for defects of the supraorbital ridge; for larger defects of the skull employment of one of the noncytotoxic alloys or metals is suggested.

DISCUSSION

DR. ERIC OLDBERG: Dr. Voris is to be complimented on the satisfactory cosmetic results he has shown. I should like to emphasize that the patient with a defect in the skull is much safer in the hands of a neurosurgeon than he would be in the hands of a plastic surgeon, whose knowledge of intracranial problems is necessarily limited. In work like Dr. Voris' there are invariably problems, such as those concerned with defects in the dura and choice of time following infection, which require specialized knowledge.

Bilateral Prefrontal Lobotomy: Perspective and Recent Survey of Results. DR. LLOYD H. ZIEGLER, Wauwatosa, Wis.

Historically, the so-called drastic therapies of the psychoses are not new. Paracelsus gave camphor to induce convulsions; Benjamin Rush offered the tranquilizer. · Malarial therapy appeared, and then, in rapid succession, insulin, metrazol and electric shock therapies. These methods of treatment tended to interest physicians in the functions of the brain, especially of the frontal lobe. All this has led to the operation of prefrontal lobotomy. A recent survey of the results of this operation in various clinics in this country and in Canada is summarized in the accompanying table.

Survey of Results of Bilateral Prefrontal Lobotomy Reported from Seventeen Clinics in the United States and Canada (January to March 1943) on Patients with a Variety of Psychiatric Reaction Types, Schizophrenia Predominating

No. of patients operated on	582
Deaths resulting from operation	11
Deaths subsequent to operation	16*
Patients rendered clinically worse by operation	8
Patients with no clinical improvement after operation	60
Patients with slight clinical improvement after operation	111
Patients showing much clinical improvement after operation	192
Patients recovered after operation; psychotic or neurotic symptoms disappeared	184
No. of patients known to be in hospital at time of study (some able to work)	265
Patients known to be outside hospital but unable to work	55
Patients known to be outside hospital, working part or full time	235

* One patient committed suicide.

As in the case of shock therapy, the first reports are usually more optimistic than they should be. Prefrontal lobotomy is a new therapeutic endeavor, and the results must be followed closely for a number of years before the permanency of the reported ameliorations can be evaluated and the types of patients most likely to be benefited can be determined.

DISCUSSION

DR. HOWARD ZEITLIN: At the Neuropsychiatric Institute, under the direction of Dr. Francis Gerty and Dr. Eric Oldberg, my associates and I undertook a study of psychiatric patients on whom lobotomies had been performed. This project entailed the study by various psychologic methods of changes in the frontal lobe following the operation. Through Dr. Percival Bailey, we have had the opportunity to operate on 5 patients since September 1942. The number was restricted to suitable patients: First, patients showing moderate degrees of mental deterioration were excluded, and, second, lobotomy was performed only after more conservative measures, such as psychotherapy and electric shock and insulin therapy, had failed to maintain improvement in the disturbed personality. Preoperative and postoperative studies were made. Special tests for function of the frontal lobe were carried out by Dr. Ward Halstead.

The first patient, with hebephrenic schizophrenia and some degree of deterioration, although not presenting the ideal conditions for operation, had a lobotomy because of the family's desire that it be tried. He has

since returned home. Although he is not yet working, he has been able to adjust, but at a lower level.

Another patient had paranoid schizophrenia, or what was thought by some examiners to be paranoia, with a fixed system of delusional ideas. For about three months after operation he improved notably. Although his paranoid ideas were still present, they remained in the background, and he no longer talked about them. On his return home, he went back to work for about a month. Recently his paranoid ideas have returned, and he is again preoccupied with them. He is being seen in the outpatient clinic each week.

The best therapeutic result was obtained in a patient whose mental illness was motivated by outstanding anxiety. Early in his life he had a psychotic episode of short duration. Reactive depressive states were frequent prior to operation. They had improved with electric shock therapy and, later, with insulin treatment, but after each course, with the return of anxiety, he failed to maintain his improvement. In the interval between episodes he displayed pronounced hypochondriacal symptoms, which finally passed into an obsessive, ruminative state, during which he spent most of the day thinking about himself. His anxiety would mount in intensity until he again passed into a depressive state. During the latter state self-destructive impulses were manifested. He tried suicide, and prior to operation he made a combined homicidal and suicidal attempt. At a conference of the entire staff the opinion was expressed that the prognosis was poor.

Almost immediately after operation the patient lost all his anxiety, as well as his hypochondriacal complaints. He is now working in a defense plant. He is fairly well adjusted and is getting along well. It is my opinion that a patient of this type is ideal for lobotomy.

Of the 5 patients operated on, 1 died of postoperative hemorrhage. However, we feel that the mortality rate should not run higher than that after operation for uncomplicated appendicitis.

It is obvious that lobotomy is not a cure-all for mental illness, but we feel it has a place in the treatment of mental disorders. So far as can be determined from our limited number of patients, it eradicates anxiety completely. This does not mean, however, that there is complete loss of the "worry center" or that the patient is reduced to a vegetative existence. Actually the personality does not change much from that prior to operation except for the changes that may be expected with the loss of anxiety. Furthermore, lobotomy does not interfere with the later use of extensive psychotherapy or psychoanalysis. In fact, the procedure makes possible psychoanalysis in cases in which the illness was formerly refractory to such therapy.

A complete report of our cases will be made later.

Dr. WARD HALSTEAD: Through the courtesy of Dr. Zeitlin, I have examined on several occasions the patient whom he described as presenting a perfect result of lobotomy. I first examined the man after operation. I agree that he presents a striking picture of apparent "normality." If the patient were here this evening I should challenge any one to pick him out of this group on the basis of his general behavior. His performance on a wide range of psychologic tests of the paper and pencil type falls well within normal limits. My category test, however, revealed both quantitative and qualitative evidence of a severe underlying pathologic state. Marked constriction of the dynamic visual field was also noted. I am continuing my study of this patient, and I prefer to postpone further comment until I am in a position to make a more complete presentation of the results.

With regard to Dr. Zeitlin's comment that the amount of intellectual impairment following lobotomy is not as great as might be expected, I can only take exception to the methods which have thus far been brought to bear on this important question.

Dr. A. EARL WALKER: I should like to add a word of caution. I am not sure that it is a good thing to turn a patient out into society without "worry centers." One should know more about the precise mental faculties of patients following prefrontal lobotomy before endorsing this procedure for the mentally ill. I doubt whether such persons will be able to carry on normally in society. It is quite true that a considerable number, as Dr. Ziegler has pointed out, have been able to return to some form of work, but it is a quite different matter for a patient to do work under supervision than for him to return to his usual occupation and carry it on successfully. Few patients have been able to do that.

Dr. CONRAD S. SOMMER: Was any attempt made to evaluate the role of other methods of treatment, such as occupational therapy or psychotherapy, in producing the results attributed to the operation?

Dr. LLOYD ZIEGLER, Wauwatosa, Wis.: Dr. Halstead has answered a question I was about to ask; Dr. Zeitlin's patient may have been immature and would have shown it if tests had been made prior to operation.

I agree with Dr. Walker about worry. It is a sign of illness to lose all capacity to worry. Of course, an excess of it annihilates the useful functions of a person, also.

In answer to Dr. Sommer's question, I have relatively little information on the adjunctive therapies that were administered to these patients. Some had been given all forms of shock therapy; some had had none. Some were subjected to psychotherapy before and after the operation; some were given shock therapy after operation and improved. From the reports that came to me I could not always tell with certainty to what reaction type the patient belonged. For that reason, I made no attempt to classify these patients.

The Diagnostic Value of Electroencephalography.
Dr. VASILIOS S. LAMBROS, Dr. THEODORE J. CASE and Dr. A. EARL WALKER.

Electroencephalography is an important and valuable aid in the diagnosis of the convulsive state and of intracranial tumors, giving evidence of alterations in the electrical activity of the brain in a large percentage of cases. Roentgenography of the skull, on the other hand, rarely shows abnormalities associated with the convulsive state. It is suggested therefore that electroencephalography, rather than roentgenography of the skull, be used as a routine procedure in the diagnosis of the convulsive state.

In cases of intracranial tumor the percentage of localizing alterations in the electroencephalogram is approximately 50, an incidence which is greater than that for alterations in roentgenograms of the skull. Moreover, localizing phenomena are present in cases in which there are no clinical localizing signs. Electroencephalography should be a routine procedure in every case in which an intracranial tumor is suspected.

DISCUSSION

Dr. CHESTER W. DARROW: I wish to congratulate the authors on their presentation of a paper which contributes to the clinical usefulness of the electroencephalogram. Was evaluation of the data based on records which included the effects of hyperventilation, and, if so, was this procedure considered necessary?

DR. PERCIVAL BAILEY: Did the electroencephalogram lead to an erroneous localization in any case?

DR. RICHARD B. RICHTER: It is gratifying to have such a statistical analysis of the value of electroencephalography. But to me these figures spell something rather different than the authors have seen in them, at least with reference to the convulsive state in general. It should be noted that the cases were selected because of a clinical history of epilepsy. In 75 per cent there were electroencephalographic abnormalities. I should like to know whether, on this account, a diagnosis of epilepsy in the broad sense of the term was excluded in the remaining 25 per cent or in any considerable proportion of this series. If not, it is difficult to see that the electroencephalogram was of real diagnostic value. Furthermore, there was no significant difference in the proportion of abnormal tracings in the cases of the organic and in the cases of the nonorganic type; when such changes did appear in cases of organic origin they were seldom qualitatively distinctive or of localizing value.

DR. VASILIOS S. LAMBROS: In answer to Dr. Darrow, all these tracings were taken with the patient breathing normally. At this time my associates and I did not employ hyperventilation.

In reply to Dr. Bailey, the electroencephalogram led to wrong localization in 3 cases; however, in all 3 of these cases there was an extensive infiltrating glioma. These 3 cases were included with the group in which positive electroencephalographic features were present but the lesion was not localized.

DR. A. EARL WALKER: Dr. Richter has presented an interesting paradox. However, I do not believe that a method of examination should be said to be of no value because it does not always enable one to make a diagnosis. Nor should the diagnosis be altered in any way because the method does not point to the diagnosis.

In many cases of tumor of the brain an electroencephalogram will present valuable evidence, but that the electroencephalogram is normal does not imply that the brain is not the site of neoplastic invasion. The same principle applies in the diagnosis of a convulsive state. In the great majority of cases of convulsive seizures the brain waves are abnormal, but in a certain number no abnormality is present; yet the diagnosis of epilepsy must be made on the basis of the clinical history.

PHILADELPHIA PSYCHIATRIC SOCIETY

HAROLD D. PALMER, M.D., *President, in the Chair*

Regular Meeting, May 21, 1943

Further Statistics on Electric Shock Therapy. DR. THOMAS WRIGHT JR.

In the past year my associates and I at the Pennsylvania Hospital for Mental and Nervous Diseases have treated 117 patients with electric shock. To these 117 patients we gave 1,006 treatments. Each person received an average of 8 treatments.

In the group with involutional psychoses 20 patients were treated. Of these, 18 (90 per cent) recovered; 1 (5 per cent) showed improvement, and 1, a woman aged 72, who had an agitated depression and had been at the hospital for ten years, showed no improvement.

In the group with manic-depressive psychosis, depressive type, 48 patients were treated. Of these, 30 (61 per cent) recovered; the condition of 9 (19 per cent) was much improved; that of 4 (9 per cent) showed improvement, and that of 5 (10 per cent) did not improve. Of the 5 patients who showed no improvement, the treatment of 1 was discontinued because of a complication affecting the respiratory tract; 1 died of a secondary infection, and 1 had a fracture as a result of electric shock. Incidentally, this was the only fracture we had during the year. (We use curare routinely.) One patient would recover from his depression only to relapse in a few days. The last patient of the group who showed no improvement only became confused.

In the group with manic-depressive psychoses, manic type, 17 patients were treated. Of these, 8 (47 per cent) recovered; 5 (30 per cent) showed much improvement; 1 (6 per cent) showed improvement, and 3 (17 per cent) showed no improvement. Most of the patients in this group had to have repeated courses of therapy.

In the group with schizophrenia 8 patients were treated. Of these, 1 (13 per cent) was much improved; 1 was improved, and 5 (60 per cent) did not improve.

In the group with psychoneuroses 8 patients were treated. Of these, none recovered; 1 (12 per cent) showed much improvement; 4 (50 per cent) showed improvement, and 3 (38 per cent) showed no improvement. The patient whose condition was much improved was homosexual, in a panic state. A follow-up study at the end of a month revealed that she was incapacitated by her psychoneurosis.

In the group with the undiagnosed psychoneuroses 15 patients were treated. Of these, 3 (20 per cent) recovered; 3 (20 per cent) showed much improvement; 7 (47 per cent) showed improvement, and 2 (13 per cent) showed no improvement. The 3 patients who recovered and 2 of the patients who manifested considerable improvement had agitated states.

These data support earlier statistics on electric shock (Smith, L. H.; Hastings, D. W., and Hughes, J.: *Am. J. Psychiat.* **100**:351 (Nov.) 1943). The rates of recovery are essentially the same except for the involutional group, for whom the rate rose from 70 to 90 per cent.

In general, agitation, depression, confusion and perplexity are the symptoms most favorably influenced by electric shock.

DISCUSSION

DR. N. W. WINKELMAN: Within the last few years my associates and I have been giving daily electric shock treatments to patients whose physical condition warrants such a heroic measure. Treatments are frequently given daily for eight to ten days, and the results have been much better than with the regimen of three treatments a week. The confusion is much greater than with the spaced treatments. At times a state is produced which resembles amentia. With patients in the manic stage of manic-depressive psychosis our results have not been good. Treatment apparently affects them only to a minor degree. It is our rule now to keep patients in the hospital two or three weeks after the cessation of shock therapy. The general statistics of the Philadelphia Psychiatric Hospital agree closely with those presented by Dr. Wright except those for the manic phase of the manic-depressive psychosis.

DR. HAROLD D. PALMER: Dr. Winkelman, do you use curare or any other means of modifying the severity of the convulsions?

DR. N. W. WINKELMAN: We do not use curare. We have had no fractures. We have the patient on a molded bed and keep the shoulders and hips down with firm pressure. Recently I have attempted to employ the dose which produces a slow, delayed reaction but does not cause the initial terrific jerking of the body.

The patient turns his head slowly, and then convulsive movements set in. If that dose can be gaged, one avoids much trouble.

Dr. HAROLD D. PALMER: What voltage is used, and where are the electrodes applied?

Dr. N. W. WINKELMAN: The reaction is a delayed general one. We begin with a low voltage and increase it gradually until the desired effect is obtained. The electrodes are placed on each side of the frontal poles.

Dr. THOMAS WRIGHT JR.: We have found the shock which produces the petit mal reactions of no value; this was particularly true for a patient in whom we did not want to induce a generalized convulsion.

Dr. JOSEPH HUGHES: How soon after admission should a patient be treated?

Dr. THOMAS WRIGHT JR.: We think that electric shock should be used cautiously. One must not forget that patients recovered before the introduction of shock therapy. We study each patient thoroughly before we consider treatment. A great many patients are rushed into electric shock who would do well under hospital care alone in a month or two.

Dr. MATTHEW T. MOORE: Many patients, particularly psychoneurotic and mildly depressed ones, respond favorably to conservative methods of psychotherapy, and much damage can be done if such persons are subjected to shock therapy. The psychic trauma, through the inference that the patient has a true psychosis, may bring about irreparable harm. There is still a difference of opinion with regard to whether morphologic change is produced in the brain. Although I have maintained that such damage does not occur, there must be some biochemical change within the ganglion cells themselves. Moreover, the indiscriminate application of electric shock to the brain over a long period may bring about changes resulting in rise in blood pressure. We have observed in a fairly large series of patients that the blood pressures have been very high.

Dr. JAMES J. WAYGOOD: My colleagues and I are treating psychoneurotic patients with electric shock, I think with benefit. The depression and anxiety disappear, even though the patient may not completely recover. Of the group so treated, only 1 was said to be "much improved"; I think that in our practice a fair percentage of patients may be considered as considerably benefited.

Role of the Cortical Respiratory Center in the Production of Respiratory Distress During Electric Shock Therapy. Dr. ROBERT G. HEATH.

In the reports on complications of electric shock, one is impressed by the large number of patients who have prolonged apnea, as well as the number of "unexplained" deaths from respiratory failure. The violent physical activity may explain cardiac failure, but the cause of deaths from respiratory failure remains unexplained, even after careful histopathologic studies. Prolonged apnea has been the only consistent complication at the Pennsylvania Hospital, and Brill and Kalinowsky reported (*Psychiatric Quart.* **16**:351 [April] 1942) that the only danger with electric shock therapy is postconvulsive arrest of respiration.

The theory of a cortical respiratory center was supported by many early investigators. Bucy and Case (*J. Nerv. & Ment. Dis.* **84**:156 [Aug.] 1936) did much to clarify this earlier work with carefully controlled experiments by stimulation of a field comparable to Brodmann's area 6b. During a craniotomy on a human patient they stimulated this area and produced complete

cessation of respiration for fifteen seconds. Wilbur K. Smith (*J. Neurophysiol.* **1**:55 [Jan.] 1938) likewise produced cessation of respiration by stimulation of this area.

In relation to the exterior of the skull, this area is roughly situated midway between the orbit and the external auditory meatus and about 1.5 inches (3.8 cm.) above a line connecting these two points. Conventional electric shock therapy frequently reveals that it lies directly in the path of the greatest strength of the electric current.

At the Philadelphia General Hospital my associates and I have been altering the position of the electrodes and have found that when area 6b is approached, respirations frequently cease completely, with resultant pronounced cyanosis. Since there is no convulsion with this treatment, coincident muscular activity cannot be considered a factor.

Recently we have been able to continue treatment in cases in which it would otherwise have been terminated by moving the electrodes nearer the vertex, approximately over the area 6a, which has been observed to have a respiration-accelerating quality. Also, with this change in position we have had no prolonged apnea.

DISCUSSION

Dr. THOMAS WRIGHT JR.: I should like to add something to Dr. Heath's statement. Only yesterday my associates and I, in treating a patient, used the large electrodes. She had a great deal of difficulty in breathing. We moved the electrodes, and she finally began to breathe well. Today we moved the electrodes farther toward the midline, and she had no difficulty in breathing.

Dr. THEODORE L. DEHNE: Of about 170 patients whom my colleagues and I have treated with electric shock, 2 died suddenly of causes which were not satisfactorily explained. The first patient, a woman aged about 50, with involutional melancholia, was in good physical condition at the time electric shock therapy was begun. Eighteen hours after her fourth convulsion she died suddenly, of what was believed at the time to be disease of the coronary arteries. Permission for autopsy was refused. The second patient, a man aged 42, who was thought to be in satisfactory health, died suddenly twenty-four hours after his third convulsion. The terminal symptoms seemed to be those of respiratory failure. Autopsy revealed no adequate cause for the death.

Dr. N. W. WINKELMAN: Some patients at the Philadelphia General Hospital who died of acute thrombosis of the coronary arteries have had no gross changes in the heart. This is because death was so sudden that the changes in the heart muscle did not become "fixed." The fact that a cause of death is not discovered does not eliminate acute coronary thrombosis.

Dr. THEODORE L. DEHNE: How does one make a diagnosis of disease of the coronary arteries if there are no changes referable to these vessels?

Dr. N. W. WINKELMAN: Often the pathologist reports "No cause for death apparent," but disease of the coronary arteries is suspected from the history. If there are no gross changes in the body or the brain, the best guess is disease of the coronary arteries, probably precipitated by electric shock.

Replacement of Convulsive Attacks by Psychoses. Dr. EARL D. BOND.

A case is presented in which a patient expressed herself in temper tantrums for twenty years and then

had epileptic attacks daily for another twenty years and periods of classic manic-depressive excitement, interrupted by short depressions, for a third twenty years.

DISCUSSION

DR. ROBERT A. MATTHEWS: In a recent article on cessation of asthmatic attacks, it was pointed out that among some 10,000 patients in state hospitals for mental disease only 5 had asthma. This observation suggests a psychosomatic relationship.

DR. O. SPURGEON ENGLISH: Dr. Bond's paper reminds me of the case of a woman aged 27 who had attacks of falling asleep. The diagnosis of narcolepsy was considered, and her disorder was treated accordingly. A depression developed which lasted a year, at the end of which there was a mild hypomanic phase. Psychoanalytic treatment, carried on for about eighteen months, disclosed many factors in her personality which seemed to be related to her depression. One of the last difficulties to clear up were the attacks of falling asleep. Since I felt that her symptoms were psychogenic, I focused attention on the emotions connected with falling asleep, and before her treatment was completed her attacks subsided. According to her last report, she had not been troubled by the spells of falling asleep for about fourteen months. I regarded the attacks as representing a momentary departure from reality, a response to a need to escape from what was going on around her, and I worked with her on that basis. I think the spells of falling asleep were connected with the factors that caused the depression. The case seems to be somewhat similar to the one Dr. Bond has described.

DR. ELMER V. EYMAN: In connection with Dr. Matthews' comments, I wish to mention the case of a woman with manic-depressive psychosis who was subject to hay fever, but who never had hay fever during the psychotic attacks. One summer her husband called to say that his wife would soon be entering the hospital again, although her condition at the time was good. When asked for his reason for this opinion, he said that as the hay fever season was well under way and his wife was free from symptoms of the disorder, he was certain that a psychotic attack was impending. The woman did enter the hospital, with a manic attack, within a short time.

DR. LAUREN H. SMITH: Some years ago I had a patient with what appeared to be paranoid dementia precox. She had fixed delusions of infidelity on the part of her husband. Finally, after she had been ill for some years, the husband did run around with another woman. When the patient learned of this from her daughter, she recovered from the apparent mental illness in twenty-four hours.

DR. WILLIAM L. LONG: During the past ten years I have interested myself in the relation of somatic complaints and depression. I have worked for ten years in the allergy clinic, and twice a week I see as many as 50 patients with asthma, hay fever and eczema. During that time I have practically never encountered a patient with a depression. The patients are annoyed that they are sick, but they are not depressed. As a rule, they are free from psychoneuroses, and it may be that their asthma gives them the mental outlet that in other persons leads to depression and neurotic symptoms.

The Electroencephalogram as a Diagnostic Aid.
DR. JOSEPH HUGHES:

Electroencephalography is indicated as a diagnostic procedure in all cases of persistent headache, fainting spells or convulsive seizures, as well as in cases of head trauma or any other condition which affects the cerebral cortex.

The normal electrical pulsations in the brain arise as the result of activity in the ganglion cells of the cortical gray matter. Normally these cells give rise to an electrical pulsation which appears in the electroencephalogram in a 9 to 11 per second rhythm with an amplitude of 10 to 30 microvolts. Abnormalities in the electroencephalogram consist of slowing in this pulsation and change in amplitude. Psychologic activity may suppress normal rhythm temporarily but does not give rise to any established change in amplitude or rate.

The electroencephalogram records electrical activity: it does not establish a clinical diagnosis. However, by interpretation of the electroencephalographic record in the light of the clinical history and the results of psychiatric and neurologic examinations, a great deal of useful diagnostic information can be obtained.

A single electroencephalogram will give positive evidence of epilepsy in about 80 per cent of cases. In this condition the frontal lobes show the greatest degree of electrical abnormality. Except for the spike-wave formations seen in some cases of petit mal, no electroencephalographic tracing is characteristic of this disease, nor can petit mal or grand mal be differentiated from each other on the basis of the electroencephalographic pattern.

Patients with behavior problems due to encephalitis or other organic causes may show abnormal tracings, the percentage depending on whether the cortex has been affected. A great deal has been written about the characteristic electroencephalographic patterns of children with behavior problems. It is an interesting corollary that a large percentage of delinquent children show no such abnormalities. In a recent survey by Hughes and Stewart of 250 boys placed in a corrective institution because of delinquency, less than 10 per cent were found to have definitely abnormal electroencephalographic tracings.

Tumors of the brain or cerebral metastasis from a carcinoma may be detected in about 90 to 95 per cent of cases in which the lesion has affected the cortex. Head trauma severe enough to produce a fracture or a concussion always results in electroencephalographic changes. These alterations may persist from three to six months after clinical symptoms have disappeared. Epilepsy is a frequent sequel of trauma. Its development may be expected in patients who fail to reestablish a normal pattern of electrical activity after an injury to the head. Dementia paralytica usually slows the cerebral pulsation and decreases its amplitude. Meningitis produces slow abnormal waves. Degenerative conditions, such as Pick's or Alzheimer's disease, also produce abnormalities. Cerebral arteriosclerosis affects the electroencephalogram to a degree which parallels the cortical involvement.

Clinical Observations on Patients with Behavior Disorders Who Show Abnormal Electroencephalograms. DR. ROBERT A. MATTHEWS.

The cases of 5 patients, with ages ranging from 6 to 20 years, who exhibited behavior disorders and abnormal electroencephalograms are reported. In addition to their calling attention to deviation of behavior as the odd expression of an underlying pathologic condition in the great integrating organ of the body, the central nervous system, these cases serve to pose several questions:

What can be done to prevent such sequelae of the virus diseases of childhood? Are these children con-

stitutionally of the chronic aggressive type, so ably discussed before this society several years ago by Dr. Gerald Pearson (The Chronically Aggressive Child, ARCH. NEUROL. & PSYCHIAT. **41**:641 [March] 1939)? If so, does the organic factor serve merely as a release of previously existing personality patterns, or is the behavior disorder the direct outgrowth of an acquired pathologic process in the central nervous system? What treatment can be instituted that may prove beneficial, and should it be psychologic or physiologic or both?

DISCUSSION

DR. HAROLD D. PALMER: In our study of behavior disorders, my associates and I have encountered 39 cases in which abnormal electroencephalograms were present. These tracings were interpreted by Dr. Hughes as indicating varying degrees of pathologic changes, ranging from simple cortical dysrhythmia to epilepsy. In many cases Dr. Hughes expressed the opinion that the tracings were similar to those obtained in cases of postencephalitic parkinsonism. The whole concept of the behavior disorder assumes a kind of related pattern, in which the qualities of the so-called postencephalitic and post-traumatic behavior disorders are predominant. Our observations lead us to the conclusion that there is a kind of dysrhythmic ideation, emotion and conduct. Some of the patients with these disorders had brain waves closely resembling those associated with epilepsy, although none had a history of attacks of grand mal, petit mal or psychomotor equivalent.

In many of these cases psychotherapy had been carried out for months or years, without benefit. The real test of the significance of these changes in brain waves is to be found in the response to treatment aimed at an alteration in the chemistry of the brain. Bradley, Jasper and others observed that amphetamine tended to correct the abnormal waves and improve the behavior in several cases. We have found this to be true. We have also employed the ketogenic diet, diphenylhydantoin sodium and small doses of phenobarbital, with good results.

It seems to me that in the kind of study which Dr. Matthews has made, and in our own work, one is crossing the borderline between the functional and the organic. One finds more and more instances in which neurotic-like states and behavior problems are related to underlying neurologic disease and consequently respond to treatment aimed at the correction of these organic and chemical disturbances, rather than to psychotherapy, which is aimed at the results of these disturbances.

ILLINOIS PSYCHIATRIC SOCIETY

FRANCIS J. GERTY, M.D., *President*

Regular Meeting, May 22, 1943

Hysteria and Malingering in Nurses. DR. I. R. SONENTHAL, Chicago.

A review of the literature on the emotional problems of nurses reveals a paucity of information. In the present paper definitions of malingering are cited (Hinsie, L. E., and Shatzky, J.: Psychiatric Dictionary, New York, Oxford University Press, 1940), and the psychology of malingering is discussed, with special reference to an article by Menninger (Psychology of a Certain Type of Malingering, ARCH. NEUROL. & PSYCHIAT. **33**:507 [March] 1935).

The case histories of 5 nurses who were patients in the medical ward are presented. The first deals with the production of hypoglycemic states which caused convulsions and led to operation for an adenoma of the pancreas; the second, with ingestion of large amounts of thyroid; the third, with the taking of phenobarbital; the fourth, with the production of symptoms diagnosed as indicative of a blood dyscrasia, and the fifth, with the apparent production of a prolonged, unexplained fever by the patient's tampering with the thermometer.

In the discussion two points are made: 1. The medical training of the patients aided them in the production of symptoms, and (2) the fact that they were medical personnel led to their not being suspected for a long time.

The relation between malingering and suicide is commented on.

In conclusion, reference is made to a reason for the physician's reaction to malingering; it is shown that in none of the cases were the goals for material gain, and the malingerer is classified with the neurotic or the psychopathic personality.

DISCUSSION

DR. FRANZ ALEXANDER, Chicago: I have little to add to this interesting paper. The case histories are convincing. It is valid to stress the presence of unconscious factors in most cases of malingering. The malingerer tries to evade some difficult situation, and there is no question that unconscious factors often play a decisive role.

On the other hand, there are known cases of malingering in which conscious motives are decisive. During World War I, among soldiers who were exhausted and wanted to get away from the front by any means, artificial infection with gonorrhea was occasionally practiced, the urethral secretion of a soldier who had a recurrence in the trenches and was sent back for treatment, being used. There may also be unconscious motives in such cases, but I think the conscious factor is predominant.

Dr. Sonenthal was hesitant about bringing up the relation of malingering to nursing. There is an interesting psychologic consideration. The nurse's psychologic situation is not an easy one. Her duty is to take care of other people all the time, whether she is equal to it or not. Whenever her dependent tendencies are aroused, they are greatly increased by her being continuously exposed to sick people who have the right to be taken care of. It is somewhat similar to the situation which is occasionally experienced in large families, in which the oldest daughter has to take responsibility for six or seven younger children. Under such circumstances one can often see her tremendous desire to be a small child, the envy of the smaller ones, and a repudiation of the imposed role of mother. Nurses are continuously exposed to a similar emotional strain. That they occasionally succumb to the temptation and wish to be sick themselves is intelligible. This wish to escape into sickness, together with the opportunity and a knowledge of symptoms, would seem to make them easier victims of malingering than many people who are not exposed constantly to this emotional difficulty. Therefore I should not be surprised if nurses did show a high percentage of malingering. However, there may be other occupations in which similar emotional conditions prevail.

DR. A. A. LOW, Chicago: Dr. Sonenthal has again emphasized the claim so frequently made that no clear distinction exists between malingering and hysteria. There are, however, the self-inflicted injuries in army service which Dr. Alexander mentioned as clearcut evidence of conscious and intentional self mutilation. That in many instances of such malingering hysteria plays no, or only a minor, part is generally agreed. Of more

significant interest is the question whether malingering is observed with respect to mental disease. It is known that Weir Mitchell took the view that mental disease may lend itself to simulation but that the simulant runs the risk of spending months or years in restraint, an event which would cancel any gain he might expect from his simulation. The simple view that war service is preferable to existence in an asylum may have been justifiable in Civil War days but is hardly applicable at present. Nevertheless, in World War I it was the consensus that mental disease cannot be, and is not, simulated. Then Dr. O. Klieneberger (*Ztschr. f. d. ges. Neurol. u. Psychiat* **71**:239, 1921) reported his experiences with German officers in a British prison camp. He trained the officers to simulate discrete psychiatric and neurologic syndromes, with the result that several of them were exchanged as invalids. Since then the controversy concerning the possibility of simulation of mental disease seems to have died down. However, it may safely be claimed that simulation of mental disease must be difficult and requires patient coaching on the part of the expert.

DR. C. F. READ, Elgin, Ill.: I have seen many cases of traumatic neuroses. For example, a laborer, perhaps 50 years old and approaching the close of his active physical life, has a bump on his head. Perhaps he feels fairly well for a few days, makes no complaint and then begins to have symptoms, usually dizziness and headache and perhaps some difficulty with vision and sleep. Such persons, as I have seen them, have all been a rather simple folk. They may have an opportunity to obtain compensation that will set them up in some little business. Perhaps they are afraid of not being able to work again as they used to, and they desire the sympathy of the family. Are these persons malingerers? How much is on a conscious level? In examination for testimony before an industrial commission one finds no objective symptoms, nor is anything noted in the neurologic examination that will substantiate the claims of the plaintiff. I wonder how far this goes beyond the desire for compensation, and whether the symptoms are not merely the continuation of those experienced immediately after the injury, for the purpose of gain. How conscious is this attempt, and what is its basis, other than the instinct for self preservation?

DR. L. H. ZIEGLER, Wauwatosa, Wis.: In the course of a similar clinical experience during the last twenty years, although in general not associated with nurses, I have occasionally seen a patient, not unlike the patients described, who struggled to conceal or camouflage the symptoms of an insidiously oncoming affective or schizophrenic disorder, which could not be diagnosed until later. Some of these patients tried to influence the physician to make a diagnosis of a physical disorder, rather than of nervousness or mental disease, which they feared. Of course, nurses would know better than others how to do this. In the light of such developments, I have felt that the word malingering should be used with caution.

DR. I. R. SONENTHAL, Chicago: In answer to Dr. Read, the choice of malingering as a reaction may easily be the subject of much discussion. When a person chooses malingering as a mode of reaction, there are definite factors in that personality (with others in the same setting) which produce that type of reaction. The choice of malingering is analogous to that of any neurosis or psychosis as a solution to a difficult situation. With respect to the selection of cases in my report, they represented a period of six years, and the nurses were not from this hospital, but were referred from

various hospitals in the city because the diagnosis of their condition was unusually difficult. I agree in principle that physicians and medical students could be included in such a study, although in the period reviewed there were no similar cases among physicians, to my knowledge.

Fundamental Concepts of Psychosomatic Research: Psychogenesis; Conversion; Specificity. DR. FRANZ ALEXANDER, Chicago.

Psychogenesis.—The term "psychogenic" refers to physiologic processes consisting of excitations in the nervous system which are perceived subjectively in the form of emotions, ideas or wishes and which can be studied by psychologic methods. Psychosomatic research deals with such processes, in which certain links in the causal chain of events lend themselves more readily, in the present state of knowledge, to a study by psychologic than by physiologic methods.

Conversion. — Essentially, a hysterical conversion symptom is nothing but an unusual innervation; it does not differ in principle from any other voluntary innervation or from such expressive movements as speech, laughter or weeping. The meaning of a conversion symptom was originally definite; it was a symbolic substitute for an unbearable emotion. It was assumed that the symptom relieved, at least to some degree, the tension produced by the repression of the unbearable emotion. It was considered a kind of physical abreaction, or equivalent, of an unconscious emotional tension.

It is not valid to extend the original concept of hysterical conversion to all forms of psychogenic disturbances of the body, particularly to those of the visceral vegetative organs. For example, in emotionally conditioned hypertension the elevation of the blood pressure is not the substitute expression of a repressed emotion, such as rage, but the normal physical accompaniment of the emotion. The elevated blood pressure does not relieve the anger in the least. It does not appear in place of an emotional tension. It simply accompanies the emotion of rage. It is an inseparable part of the total phenomena called rage. The same thing obtains for other vegetative disturbances. The pathologic nature of such vegetative disturbances consists in their chronicity. There are chronic, unrelieved emotional tensions which cause chronic vegetative disturbances. The quality of the physiologic response is normal; only its chronic nature is morbid.

Therefore it seems advisable to differentiate between hysterical conversion and vegetative neurosis. Their similarities are superficial; both conditions are psychogenic. The mechanisms involved, however, are fundamentally different, both psychodynamically and physiologically. A hysterical conversion symptom is an attempt to relieve an emotional tension in a symbolic way; it is a symbolic expression of a definite emotional content. This mechanism is restricted to the voluntary neuromuscular or sensory perceptive systems, the function of which is to express and relieve emotions. A vegetative neurosis consists of a psychogenic dysfunction of a vegetative organ which is not under control of the voluntary neuromuscular system. The vegetative symptom is not a substitute expression of the emotion but its normal physiologic component. It is assumed that for every emotional state there is a corresponding distribution of vegetative innervation. When the organism is ready to fight, the vegetative organs are relatively relaxed, whereas the muscular system and the lungs are in a state of preparation for activity. The emotional attitude accompanying and preceding intake of food is, again, accompanied by a different distribution of vegetative tonus. One type of vegetative disturbance occurs as a result of an emotional retreat

from strain. If, for example, the patient with a neurosis referable to the stomach breaks down under an excessive load of responsibility, he recoils from his habitual over-activity and assumes the vegetative mood of the state that accompanies digestion, to which his alimentary tract reacts with continuous hyperactivity. According to all indications, an outwardly directed, active aggressive state is associated with a sustained excess of tonus of the sympathetic-adrenal system, from which the person when exhausted may retreat into the opposite attitude, in which the tonus of the vagoinsular system is in-creased. This recoil from exaggerated outward activity and strain may be called "vegetative retreat." It is characterized by increased tonus of the parasympathetic system, possibly associated with simultaneous relaxation of sympathetic-adrenal tonus. This may assume differ-ent forms, consisting in some hyperactivity of visceral organs as a result of parasympathetic excitation, such as hypersecretion and hypermotility of the stomach, diarrhea or psychogenic hyperinsulinism (psychogenic hypoglycemia).

Specificity.—According to one school of thought, there is no specficity of correlation. Any emotional tension may influence any vegetative system. The choice of the symptoms may depend on the history of the patient and on his constitution. The other heuristic assumption, which has guided the work of the Chicago Psycho-analytic Institute, is that the physiologic response differs with the emotional tension and that, consequently, vege-tative dysfunctions result from specific emotional con-stellations. It was found, for example, that symptoms of gastric neurosis have a different psychologic setup from those of emotional diarrhea or constipation; patients with cardiac disorders differ in their emotional background from asthmatic patients. Hypertensive pa-tients, again, have a different psychodynamic constella-tion. To what extent constitutional factors influence the picture and to what extent a preexisting organic pathologic condition or sensitivity is responsible are questions to be decided by further clinical studies.

DISCUSSION

DR. WARREN S. MCCULLOCH, Chicago: Most, and first, consideration should be given to Dr. Alexander's opening statement concerning the elimination, once and for all, from the publications of psychosomatic medicine of any discussion of problems of the relation of mind and body. I feel like giving three cheers for the in-different monism that underlies such a comment. There is a dichotomy in medicine which has grown increas-ingly. It is a consequence of the division into special-ties. The psychiatric, particularly the psychoanalytic, approach has produced one group; the organic approach to the physiology of particular organs and disease processes has made organicists of another group. It has become difficult for these two groups to talk to each other. I am afraid that there is still in the minds of most persons here, and will be for years, that difficulty which concerned, and still concerns, many thinking people—the dichotomy of mind and body. There is still the attempt to explain "the leap from psyche to soma."

Dr. Alexander uses two types of terminology: the one when he speaks of mental affairs and the other when he speaks of physical affairs. It is appropriate that he should speak in mental terms of psychologic processes, for these exhibit ideas and intentions. It is equally appropriate that he should speak in physical terms of bodily processes, for these exhibit matter and energy; the difficulty, however, is that no one has ever managed to conceive how the patient—the monad—can have such a divorcement of the psychologic and the

physiologic aspect of his nature. I may be thought to be exaggerating the difficulty, but there have appeared within the last few years two books which tilt at the same windmill. In one, entitled "Man on His Nature" (London, Cambridge University Press, 1938), Sherring-ton, the marvelously honest physiologist, attempts to make head and tail of the relation of mind and body, but is frustrated because in that world "mind goes more ghostly than a ghost." In the other, entitled "The Place of Value in a World of Fact," by Wolfgang Köhler (the founder of gestalt psychology), one is con-vinced that the author, in spite of his endless searching, has not found the place of value in the world of fact. Such was the unsatisfactory state of the theory until recently.

However, there recently has appeared an article by Rosenblueth and collaborators (*Philos. Sc.* **10**:18, 1943) which gives a general presentation of systems responding to the outside world, that is, to the strains or impulses impingent on such systems from the out-side world. Systems are classified according to the way in which they respond. In particular, the authors discuss the type of behavior characteristic of sys-tems in which the system so responds as to decrease the difference between the impinging disturbance and the energy already present in the system. Certain of these systems depend on disturbances traveling in closed paths, or circuits, and respond in such a way as to decrease the difference between the adventitious dis-turbance and the disturbance traveling in the closed system. Two such familiar devices are the self-tuning radio, which seeks its station, and the self-directing torpedo, which hunts its prey. Engineers call such devices servile; psychologists call them appetitive. Psy-chologists refer to such behavior as motivated, goal directed or purposeful, and organisms are known to contain systems of the type in question. In other words, organisms and all such devices have those aspects of behavior which are utilized in the definition of pur-posiveness. One can then define in purely mechanistic terms (or have a purely mechanistic conception of) the attempt to reach any goal.

At present the other mental aspect of behavior—its ideational or rational, formal or logical aspect—is com-ing to the fore. Work on this phase was begun some years ago in the department of mathematical biophysics of the University of Chicago and should be coming to fruition in the next year or two. Under these circum-stances, I am not surprised that the *Journal of Psycho-somatic Medicine* should receive articles on the problem of the relation of mind and body. One does resent the existing hiatus between the mental and the physical terminology. The problem is today being attacked in a realistic fashion. So while one does at the moment think of the "leap from psyche to soma," one is busy bridging the gap between mental and physical processes. To this audience it is interesting that such a bridge is being formed through the demonstration that the sys-tems which are like the nervous system necessarily show those aspects of behavior that are called "mental" —namely, ideas and purposes. So much for the first part of Dr. Alexander's paper.

The second question which he has raised and answered concerns the distinction between those structures which are under voluntary control, and hence can be used relatively easily in symbolic fashion because they deal with the outside world, and those structures which are not under voluntary control or of use in handling the outside world, but readjust the immediate environment of the nervous system to its demands—the autonomic nervous system and the glands under its control. This point needs little discussion, for it is clear that Dr.

Alexander has put his finger on one of the crucial differences between the two systems, both in their function and in their abuse, or disease. The first system is as flexible as man's adjustments to the external world, and the second, as stereotyped as man's primordial emotions.

Here another consideration prompts me to ask a further question. Neurophysiologists originally thought in terms of mere conduction. Later they came to think in terms of reflexes. Today there is a growing tendency to think in terms of closed circuits. In the case of the so-called voluntary nervous system, the circuit closes through the world outside the organism and forms the link between one's actions and one's resultant sensations. In the case of the autonomic nervous system, the circuit closes within the body by means of glands and smooth muscle, the action of which, in turn, affects the nervous system. But there is a third possibility; I wonder whether Dr. Alexander has yet considered it. There is within the nervous system itself an enormous number of closed circuits. My question is whether these closed circuits may not themselves prove an even more fruitful field for psychiatric study than any one has hitherto dreamed.

Dr. Alexander's last question concerned the relation of the autonomic nervous system to the emotions. He asked to what extent a specific emotion gives rise to a specific autonomic outflow and suggested that the relation was relatively constant. In this I heartily agree with him. Inevitable specificities of nervous energies are involved in the emotions. Even particular pathways in the nervous system are involved in particular emotions. These pathways are related definitely to particular organs and to particular glands and smooth muscles. Thus one must expect particular organs to be involved in particular emotions. The other side of the question obviously depends on the organs of the particular pathways, particularly if they are defective. Inherited bent and learning may determine what particular emotion the patient experiences under given conditions, but when all is said and done, I heartily agree with Dr. Alexander that a particular emotion is related to an autonomic discharge to particular organs, though neither the emotion nor the discharge is completely determined by that relation.

Dr. Meyer Solomon, Chicago: First, I wish to compliment Dr. Alexander on his critical and common sense approach to this whole problem. Many psychiatrists, like himself, have been battling with the problem of mind and body, struggling to get a satisfactory clinical approach. I wonder whether the term "psychophysiologic medicine" or "organismic medicine" is not preferable to "psychosomatic medicine."

One of the problems is the use of the terms mind and psyche without definition.

The following clinical approach seems useful and practical: For practical purposes bodily activities can be divided into three types: psychologic; skeletal (voluntary, ambulatory, sensorimotor, postural and projicient), and visceral (involuntary and vegetative). Ordinarily, these levels of activity are interrelated, interdependent and integrated into a unit. The psychologic level may be referred to as psychologic or mental and includes such special bodily activities of an internal, subjective nature as thinking, feeling, wishing, reasoning and imagining. It has been customary to use the generic term "the mind" or "the psyche" to refer to this special group of bodily activities, and then the mistake is made of speaking of "the mind" as if it were a separate entity which is causative and does things. In fact, there is no such entity as "the mind";

there are mental, or psychologic, activities. Psychosomatic, or psychophysiologic, or organismic medicine, which deals with what is commonly referred to as the influence of "the mind" on the body, is concerned with the interrelation of the three levels already mentioned, namely, the psychologic, the skeletal and the visceral. Dr. Alexander has discussed critically the question of the relation of the psychologic to the skeletal and the visceral level. This brings up the question of immediate versus remote and direct versus indirect effects. An immediate effect is emotional behavior, with psychologic, skeletal and visceral upheaval; a remote effect is loss of weight following poor sleep and poor appetite of psychologic origin; a direct effect is voluntary movement of the skeletal system (head, trunk, extremities), and an indirect effect is vegetative activity for the maintenance and support of voluntary activities. This brings up such problems as that of so-called voluntary acceleration of the heart rate and the relation to sensory function.

In his presentation, therefore, Dr. Alexander has expressed a sensible, basic point of view with respect to fundamental problems in this complicated field of medicine.

Dr. Franz Alexander, Chicago: I wish to thank all the discussants for their instructive comments. I shall clarify one point only. Let it be assumed that two chess players are sitting opposite each other, and that I am watching their playing. I can understand their moves through certain logical deductions; that is, I can describe their motivations in psychologic terms. Chess playing is a rather complicated procedure, but the motives of the players in making the moves can be reconstructed with complete precision. Now let it be assumed, for example, that fifty years hence one will be able to describe with equal precision all the neurophysiologic processes which took place in the brain of the players while they are making their different moves. Then, on one side, we shall be able to describe the mental processes taking place in the minds of the players in psychologic terms and, on the other, the same processes in neurophysiologic, and ultimately in physicochemical terms. Both descriptions will represent complete causality: the one psychologic and the other physiologic.

Psychosomatic medicine deals with processes which, in the present state of knowledge, can best be approached partially by physiologic and partially by psychologic description.

One cannot use at present a homogeneous language in dealing with certain conditions. For example, in the case of psychogenic hypoglycemia one must describe the causal factors in psychologic terms, namely, those depressive ideas which are responsible for the vegetative innervations which lead to hypoglycemia. Perhaps at some future time these emotional factors may be described in physiologic terms and a homogeneous language used. How can that be done today with such complex psychologic phenomena as are involved when a patient becomes depressed because his sweetheart has left him? How can one describe in physicochemical terms the injury to his pride, his loss of interest in everything, his resentment? At present the only possible procedure is to deal with the emotional factors in psychologic terms and its physiologic effects in physiologic terms. In the future, with progressing knowledge of the physiology of the brain, a homogeneous physiologic description is conceivable, but even then it appears questionable whether one can dispense with detailed psychologic descriptions in an understanding of the patient's complex human relationships.

Book Reviews

The Boy Sex Offender and His Later Career. By Lewis J. Doshay, M.D., Ph.D. Price, $3.50. Pp. 217. New York: Grune & Stratton, Inc., 1943.

Dr. Doshay, psychiatrist to the Children's Courts in New York city, has written an important and needed book describing his findings in 256 cases of male juvenile sex offenders studied and treated at the clinics of the courts between June 1928 and June 1934. Sexual offenses accounted for less than 5 per cent of the acts for which delinquent boys were brought to court. At the time of the clinic study the ages of the boys ranged from 7 to 16 years, and at the time of writing they varied from 16 to 28 years. Seventy-five per cent of both groups were in the age range from 12 to 15 years, and the average age for the whole group was 13.6 years. The follow-up study was made from six to twelve years after the original court appearance. Female sex delinquents were not included in this study, and all mentally defective sex offenders were excluded. The boys were divided into two groups, one being the so-called primary group of 108, who were in court solely because of sex delinquencies, and the second the mixed group, of 148, whose delinquencies included sexual and other antisocial acts.

The author compares the two groups from the standpoint of family and home factors, factors concerned with the personalities of the parents, community factors and inherent traits in the boys, including temperament and behavior. His investigations reveal that children in the primary group came from homes of higher income, better housing and higher educational status.

With respect to the personalities of the parents, special emphasis was placed on such items as alcoholism, drug addiction, court records and desertion. It was found that the outstanding defects among the fathers in the primary group were alcoholism and desertion, which occurred in 37 per cent, whereas in 63 per cent of the fathers of the mixed group alcoholism, desertion, criminality, immorality and cruelty were noted. Poor community factors—for example, a bad neighborhood; unhealthy forms of recreation, such as poolrooms; maladjustment at school; occasional or no church attendance, and hazardous vocational interests, such as selling papers at night, shoe shining or entertaining in grills or saloons—were found for only 24.3 per cent of the primary group, as compared with 75.7 per cent of the mixed group.

In a study of the temperament and behavior of the boys, it was found that disorders such as surliness, callousness, cruelty, restlessness, stubbornness and aggressiveness appeared six to ten times as often in the mixed group as in the primary group. Of the types of sex offenses, the only item of notable difference was the occurrence of 12 instances of incest with sisters in the mixed group and of only 1 instance of attempted incest in the primary group. Otherwise, the types of sex offenses were the same and included all acts, such as fellatio, sodomy, exhibitionism, peeping and heterosexual experiences. Serious physical defects (tuberculosis, heart ailments, deafness and severe malnutrition) were present in 11.1 per cent of the primary group and in 3.4 per cent of the mixed group. Glandular defects were found in only 4.3 per cent of cases. The author emphasizes that delinquency, sexual or general, is not due to glandular disorders.

In the follow-up study, there were only 10 known instances of sex violations among 8 adult members of the mixed group and no instance of sex violations in the primary group. However, 2.8 per cent of the primary group and 25 per cent of the mixed group were involved in delinquencies in their adult life, including burglaries, assault, arson and forgery.

Dr. Doshay concludes that male juvenile sex delinquency is self curative, provided "the latent forces of shame and guilt, inherent in the moral-cultural pattern, are properly stimulated into action." He further points out that the outlook for juvenile delinquency in general is much better than that indicated by the works of the Gluecks, Healy and Bronner. Dr. Doshay's findings are in close accord with the results of follow-up studies in the Bellevue Hospital adolescent ward. Dr. Doshay further indicates the close cooperation between the judges of the Children's Courts and the physicians in following out recommendations for treatment, an observation which has also been made in the Bellevue studies.

It is my impression that the book in general is a real contribution to knowledge, not only of sexual delinquency but of juvenile delinquency in general, and that it is a book of definite value to probation officers, social workers, teachers and psychiatrists. It indicates that the prognosis, even for the most severe forms of juvenile delinquency, is much better than that indicated by many investigators. This book should serve as an added impetus to all workers in the field of child guidance and should spur one on to increase medical and social facilities for the treatment of these unfortunate youngsters.

Manual of Industrial Hygiene and Medical Service in War Industries. Prepared by the Division of Industrial Hygiene, National Institute of Health, United States Public Health Service. William M. Gafafer, D.Sc., editor. Price, $3.00. Pp. 508. Philadelphia: W. B. Saunders Company, 1943.

The rapid growth of industry necessitates a related increase in industrial health practice. The need for this volume was clearly foreseen by the Committee on Industrial Medicine of the Division of Medical Sciences of the National Research Council, and the preparation of the book was entrusted to the United States Public Health Service. Special chapters were written by an outstanding group of experts.

The volume is divided into three parts. Part 1 is concerned with the organization and operation of facilities. This portion of the book is headed by an excellent chapter on the war's influence on industrial hygiene, written by J. J. Bloomfield. Other chapters cover the problems of plant medical facilities; organization of a plant medical department; medical, nursing and dental services, and the organization of plant emergency medical service and its integration with that of the community.

Part 2 is concerned with the prevention and control of disease in industry. Here special chapters are devoted to the problem of occupational disease, occupational derivates, engineering control of air contamination, medical disease control, venereal disease control, health education, industrial psychiatry, industrial fatigue and nutrition in industry. This section is well done. Another portion of the volume is concerned with plant and community sanitation, heating, ventilation and illumination problems.

The third portion of the volume is concerned with the manpower problem, and careful consideration is given to problems of the maximal use of manpower, women in industry and absenteeism.

This book is highly recommended as a timely volume on industrial medicine. It is the best of its kind, is exceedingly well written and should be of great interest to every physician.

Convulsive Seizures: How to Deal with Them, a Manual for Patients, Their Families and Friends. By Tracy J. Putnam, M.D. Price $2. Pp. xv plus 168. Philadelphia: J. B. Lippincott Company, 1943.

This is a small book, but full of meat, and expressed in unusually readable terms. It is well within the capacity of the layman to understand; yet it includes the best of current thought on this important subject. The author is particularly to be commended for sounding a hopeful note without at the same time indulging in any Pollyanna attitude. He shows that while great advances in the knowledge of the disease have come about through the researches of the past few years, the investigations to come are even more important. He calls vigorously for greater public interest in the plight of persons unfortunate enough to have seizures, and at the same time urges the sufferers to help themselves. "Much remains to be done," he asserts, and proves this by pointing out in almost every chapter where the advances of the future may be anticipated.

The plan of the book is excellent. It is written not as a medical text, but strictly from the standpoint of the individual patient and for his benefit. Yet it takes up in succession causes, diagnosis, treatment and prognosis of convulsions, references to the literature and special problems of interest to lawyers and legislators. Brief summaries, almost aphorismic, are enclosed in boxes in connection with each chapter, so that he who runs may read. Sane and sensible directions for the management of the individual attack; serious, yet hopeful, suggestions for the planning of a career for the afflicted person; references to more elaborate treatises, with cautions against too much indigestible reading and any self medication—these are features that make this small volume one that can be placed in the hands of the patient with all reasonable assurance that it will be helpful.

News and Comment

THE AMERICAN BOARD OF NEUROLOGICAL SURGERY

Dr. Wilder Penfield, of Montreal, Canada, has been granted a certificate without examination by the American Board of Neurological Surgery.

THE HUMAN PYRAMIDAL TRACT

IX. EFFECT OF PARALYSIS PRODUCED BY CEREBRAL TUMORS ON AXONS OF THE PYRAMIDS

A. M. LASSEK, M.D., PH.D.

CHARLESTON, S. C.

The many investigators of the human pyramidal system have been handicapped in not being able either to produce experimentally or to obtain from autopsy material a pure lesion of the corticospinal tract. Until such an isolated lesion can be studied, it is difficult to evaluate what the exact role of this bundle may be in man. Many of the lesions affecting the corticospinal tract occur high up in the central nervous system, in the region of complex, and as yet largely unknown, structures. It seemed possible that, irrespective of the etiologic and pathologic factors, the pyramidal axons might not be completely destroyed in all cases of unilateral paralysis, whether the latter is called hemiplegia or hemiparesis or something else. How many axons, if any, must be missing in the pyramid to produce muscular dysfunction or the abnormal Babinski sign I have not found stated in the literature. With these considerations in mind it was decided to study the effect of paralysis produced by cerebral tumors on the fiber components of the pyramids, a silver stain for the axons serving as a criterion of fiber loss.

MATERIAL AND METHODS

This investigation would not have been possible except for the cooperation of Dr. Joseph Globus, of Mount Sinai Hospital; Dr. Abner Wolf, of the Neurological Institute, and Dr. Charles Davison, of Montefiore Hospital, all of New York. All the clinical information and pathologic diagnoses were obtained from reports in the neuropathologic departments of these institutions.

Of 119 cases in which the medulla oblongata was suitable for study, selected from about 2,000 cases of disease of the brain and cord, 60 were from Mount Sinai Hospital, 49 from the Neurological Institute and 10 from Montefiore Hospital. Only cases were chosen in which there was exhibited one or more of the classic signs of involvement of the pyramidal tract, especially the Babinski sign. Thus, in 100 cases the Babinski sign was present; in 4 cases, the Hoffmann sign, and in 2 cases, the Chaddock sign; in 13 cases no mention of the presence of any of these abnormal reflexes was made. In 34 cases combinations of signs were mentioned,

such as the Babinski and Chaddock signs or the Babinski, Oppenheim and Hoffmann signs. In 62 cases the abdominal reflexes were absent on the affected side. In 79 cases the patients were males and in 38 females; in 2 the sex was not mentioned. The average age was 47.7 years. The mean duration of symptoms was six months, with a variation from nine days to three and a half years. In many cases operation was performed shortly after a diagnosis of cerebral tumor was made.

The terms used by the clinicians in diagnosis of the paralyses in this series were as follows: hemiplegia, in 35 cases; hemiparesis, in 34 cases; muscular weakness, in 10 cases; complete unilateral paralysis, in 6 cases; pyramidal tract signs, in 5 cases; dragging foot, in 5 cases; difficulty in walking, in 4 cases; falling, in 4 cases; staggering, in 2 cases; heaviness of extremities, in 1 case; inability to move extremities, in 1 case; inability to walk, in 1 case; progressive motor impairment, in 1 case; contracture with paralysis, in 1 case; involvement of a lower limb, in 1 case; flaccid paralysis, in 1 case, and aphasia with vesical and rectal disturbance, in 1 case. In 5 cases the diagnosis was not recorded. In 90 cases the cerebral tumor was primary; in 12 cases the tumor was a meningioma, and in 17 cases it was a secondary carcinoma. The large majority of the primary tumors were of the following types: glioblastoma multiforme, glioblastoma, spongioblastoma and astrocytoma.

The lesions involved all parts of the cerebrum. Of the 119 cases, a single lobe was affected in 47, a combination of lobes in 51, the subcortical tissue alone in 17, the floor of the skull in 1 and both hemispheres in 1; in 2 cases the pathologic process was questionable. The frontal lobe was involved alone in 15 cases, the temporal lobe in 16, the parietal lobe in 13 and the occipital lobe in 3. Two lobes were affected in 37 cases, three lobes in 13 and four lobes in 1. Alone or in combination the frontal lobe was involved in 47, the parietal lobe in 48, the temporal lobe in 40 and the occipital lobe in 24. According to the neuropathologic reports, no involvement of the frontal lobe, the seat of the so-called motor cortex, was apparent in 72 cases.

All of the brains from which the medullas were obtained had been kept in jars containing a dilute solution of formaldehyde U. S. P., the time of fixation varying from a few days to sixteen years. Subsequently, cross sections of all the medullas were stained by Davenport's original silver nitrate method after fixation in the solution of formaldehyde, a method which is specific for axons.[1] This technic gave rather uniform results in spite of the variations in time of fixation. The possibility that glial fibers were stained was ruled out.

The amount of damage to the specimens which showed obvious loss of pyramidal fibers was determined by measuring the square areas of the abnormal and the normal sides, sampling the tract with a Whipple square and then computing the loss.

1. Davenport, H. A.: Staining Nerve Fibers in Mounted Sections with Alcoholic Silver Nitrate Solution, Arch. Neurol. & Psychiat. 24:690-695 (Oct.) 1930.

RESULTS

In only 17 (14.3 per cent) of the 119 cases was there observable evidence of destruction of the pyramidal tract. In 14 of these the patients were males, and in all 17 the average age was 43.4 years. In 9 (7.6 per cent) partial and in 8 (6.7 per cent) complete destruction was observed.

Either by coincidence or by predilection, all the patients who exhibited complete loss of pyramidal fibers were males. In this group the average age was 39.4 years. Absence of the superficial abdominal reflexes was recorded in 4 cases of these 8 cases, the Babinski sign was present in 6 cases and the Hoffmann sign in 1 case, and the presence of pyramidal tract signs was mentioned in 1 case. The clinical diagnoses were as follows: weakness, 1 case; complete hemiplegia, 3 cases; complete hemiparesis, 1 case; paralysis, 1 case; complete paralysis, 1 case, and contracture with paralysis, 1 case. The lesions were widespread; more than one lobe was always involved, including the frontal lobe and usually subcortical elements.

The estimated amounts of axonal loss in the 9 partially damaged pyramids were as follows: 5, 25, 40, 50, 50, 50, 75, 75 and 80 per cent. The lesions in these cases likewise were rather widespread, and in only 1 case was one lobe of the brain alone involved, in this instance the parietal. The pyramidal tract in this case showed damage to about 50 per cent of the fibers. In most cases the frontal lobe and subcortical structures were invaded. In this series of cases, 5 patients were males and 3 females, and the sex of 1 was not mentioned. In 6 cases the sign of Babinski was present; in 1 case pyramidal tract signs were recorded, and in 2 cases the evidence was questionable. In 4 cases the diagnosis was hemiplegia; in 2 cases, hemiparesis; in 1 case, pyramidal tract signs; in 1 case, weakness, and in 1 case, paralysis. In none of the cases of partial damage to the pyramidal tracts were isolated or restricted parts of the pyramids affected; degeneration was scattered and uniformly distributed.

In the other 102 cases, I was unable to detect any loss of fibers, gliosis or decrease in area in the pyramids. To be fair, when one is counting so many axons and using a silver stain, one might miss some less easily detected fibers. A Marchi stain, for instance, might show the presence of degenerated fibers. It appeared, however, that the individual damage in these cases was minimal, or possibly absent. The pathologic reflexes observed in this series of 102 cases were as follows: the Babinski sign, in 88 cases; the Hoffmann sign, in 3 cases, and the Chaddock sign, in 2 cases; in 9 cases there was no record of abnormal reflexes. There were also combinations of these signs. In 28 of the cases the condition was diagnosed as hemiplegia, in 31 as hemiparesis, in 8 as weakness and in 5 as complete unilateral paralysis; in 28 cases it was designated by a less specific term. In 66 cases the patients were males and in 38 females, and in 1 case the sex was not reported. Practically every part of the cerebrum was affected; in one third of the cases the frontal lobe was involved. Since often individual gyri of the brain were not named with respect to the extent of the tumor, I cannot say how often the precentral convolution was injured.

COMMENT

On the basis of the material and methods utilized in this investigation, it appears that motor deficit in man, with one or more of the classic signs of damage to the pyramidal tract, can be produced with little or no loss of the axis cylinders in the pyramid. Of this series of 119 selected cases of tumor of the cerebrum, complete axonal loss was shown in 6.7 per cent and partial destruction in 7.6 per cent, and in 85.7 per cent there was no observable change. In the last group it is possible that loss of some fibers could not be detected with the silver stain alone, but such loss must have been minimal.

Various terms were used by the clinicians to describe motor deficit in these cases, and it is difficult to correlate them with destruction of the pyramidal tract. For instance, the terms "weakness" and "hemiparesis" were employed to indicate the amount of motor deficit in 2 cases in which microscopic examination showed complete destruction of the axons in the pyramid. In all, seventeen expressions were used to describe muscular dysfunction. It would be no easy task to standardize the terminology so that one term would accurately express a certain degree of paralysis. Since the physiologic motor deficits were studied by a number of clinical observers, it is possible that some of them did not have in mind disease of the pyramidal tracts. The individual terms employed would have meaning only for the examining neurologist and could not be evaluated correctly by another person, least of all by one not connected with the hospital. It should be mentioned, also, that in some instances the records of the history and the physical examination were not as complete as one might desire. In some instances the Babinski sign was evidently elicited only once without further recorded trials; so there is a chance that in some cases this sign may have been transient. It can be said, however, that in general the cere-

bral tumors in this series of cases caused motor dysfunction severe enough to result in incapacitation. The cases were carefully selected from about 2,000 cases of disease of the brain and cord, and I believe they represent the least equivocal specimens that can be obtained from available stored material. The criteria primarily used for selection of the cases were the classic signs of damage to the pyramidal tract, especially the Babinski sign, rather than the diagnoses made by the clinicians. It is realized that the ideal situation would be one in which a single skilled investigator followed suitable cases from beginning to end, and it is hoped that this may eventually be done.

In this series, a tumor mass in any part of the cerebrum apparently produced motor deficit with either a transient or a permanent Babinski sign. In many cases the frontal lobe was not involved. If these observations are correct, it should be difficult to localize tumors on the basis of so-called pyramidal tract signs alone. In order that the axons of the pyramidal bundle may be completely destroyed, rather widespread involvement of the brain appears necessary, and in almost all cases subcortical structures were implicated. Von Monakow[2] observed that in man destruction of a whole hemisphere seems necessary for destruction of all the fibers of the pyramidal tract. The recent experimental investigations of Häggqvist; Hoff and Hoff; Kennard; Lassek; Lassek and Rasmussen; Minckler and Klemme; Peele, and Spiegel, Weston and Oppenheimer[3] have indicated that the origin of

2. von Monakow, C.: Zur Anatomie und Physiologie der Pyramidenbahn und der Armregion nebst Bemerkungen über die sekundäre Degeneration des Fasciculus centroparietalis, Neurol. Centralbl. **34**:217-224, 1915.

3. Häggqvist, G.: Faseranalytische Studien über die Pyramidenbahn, Acta psychiat. et neurol. **12**:457-466, 1937. Hoff, E. C., and Hoff, H. E.: Spinal Terminations of the Projection Fibers from the Motor Cortex in Primates, Brain **57**:454-474, 1934. Kennard, M. A.: Corticospinal Fibers Arising in the Premotor Area of the Monkey, Arch. Neurol. & Psychiat. **33**:698-711 (April) 1935. Lassek, A. M.: The Pyramidal Tract: The Effect of Pre- and Postcentral Lesions on the Fiber Components of the Pyramids in the Monkey, J. Nerv. & Ment. Dis. **95**:721-729, 1942. Lassek, A. M., and Rasmussen, G. L.: The Human Pyramidal Tract: A Fiber and Numerical Analysis, Arch. Neurol. & Psychiat. **42**:872-876 (Nov.) 1939. Minckler, J., and Klemme, R. M.: Role of the Premotor Cortex in Human Motor Activity, Proc. Soc. Exper. Biol. & Med. **53**:264-265, 1943. Peele, T. L.: Cytoarchitecture of Individual Parietal Areas in Monkey (Macaca Mulatta) and the Distribution of Efferent Fibers, J. Comp. Neurol. **77**:693-723, 1942. Spiegel, E. A.; Weston, K., and Oppenheimer, M. J.: Postmotor Foci Influencing the Gastrointestinal Tract and Their Descending Pathways, J. Neuropath. & Exper. Neurol. **2**:45-53, 1943.

the pyramidal tract may involve more than area 4. If these current observations are correct, more extensive damage to the cortex would be expected to cause complete destruction of the pyramidal tract.

In cases of cerebral tumor it is well known that the intracranial pressure is increased and that there may be interference with the blood supply. If increased cerebrospinal pressure is a factor, it is difficult to see why or how it should single out the pyramidal tract alone and leave unaffected axons belonging to other systems. It is unlikely that increased pressure would cause death of the neurons. The part it plays, if any, might be one of depression of nerve activity. On the other hand, if there is interference with the vascular supply to the so-called motor cortex due to lesions remote from this area, it is probable that death of the neuron might occur in cases of chronic disturbance in the blood supply. These suggestions, however, are mere speculations.

There is evidence that paralysis and the sign of Babinski may occur in many cases with little or no destruction of pyramidal axons. Since the stain employed is selective for axis-cylinders, I am unable to state, at this stage, whether a technic for myelin sheaths would confirm the present observations. Further studies on this phase, with stains for myelin sheaths and fats, are in progress in this laboratory. One should keep in mind, perhaps, that in some of these cases the cells of origin of the pyramidal tract, or the fibers arising from them, may be temporarily deprived of function by pressure, anoxemia, narcotic poisoning or some other phenomenon. These factors might be suggested to explain a transient Babinski sign. I wish to be conservative and cautious in advancing any radical opinion concerning the pyramidal system.

CONCLUSIONS

Within the limits of the materials and methods used in the present investigation, there is some foundation for the following conclusion: In cases of cerebral tumor, unilateral motor deficit, with one or more pyramidal tract signs, may occur with little or no loss of axons in the pyramidal tract. In 8, or 6.7 per cent, of 119 cases was destruction complete. Apparently, tumors located in any part of the cerebrum may produce motor difficulties with signs of damage to the pyramidal tract. In this series the tumors which caused complete destruction were widespread. It is difficult to correlate the terminology employed in describing paralyses with the destruction of the pyramidal tract.

PATHOLOGIC FEATURES OF HERPES ZOSTER

A NOTE ON "GENICULATE HERPES"

D. DENNY-BROWN, M.B., AND RAYMOND D. ADAMS, M.D.

BOSTON

AND

LIEUTENANT (JG) PATRICK J. FITZGERALD (MC), U.S.N.R.

Herpes zoster, or zona, is a common nervous disease known since ancient times but still possessing many enigmatic features. From the contributions of von Bärensprung,[1] Head and Campbell,[2] Lhermitte and Nicolas[3] and many others the broad outlines of this condition may be sketched.

The present day conception of herpes zoster embraces the following assumptions and facts: The disease is probably due to a filtrable virus, similar to, if not identical with, that of varicella, which provokes an acute inflammatory reaction in isolated spinal or cranial sensory ganglia, the posterior gray matter of the spinal cord and the adjacent leptomeninges. The clinical manifestations are a vesicular cutaneous eruption, radicular neuralgia and, less often, segmental palsies and sensory loss.

The association of the cutaneous eruption with a disease of the peripheral nerves was brilliantly deduced from clinical data by von Bärensprung[1a] in 1861, and in 1862 he described in considerable detail the inflammatory changes in a dorsal root ganglion and related portions of the spinal nerve in a case in which autopsy was performed (von Bärensprung[1b]). Head and Campbell[2] indicated the necrotic and limited character of the ganglionic lesions and the patchy inflammation of the neighboring ganglia. The cause of this ganglionic necrosis and its relation to changes in the neighboring ganglia and nerves, particularly the motor nerve root, are still obscure. For this reason further observations are desirable.

In view of the large number of sensory ganglia which may be involved the clinical possibilities are manifold. In the region of the cranial nerves two special syndromes are frequent, namely, "ophthalmic herpes" and "geniculate herpes." The pathologic changes in the gasserian ganglion in the former syndrome were described by Head and Campbell.[2] The combination of paralysis of the facial nerve and auricular herpes, with or without deafness, tinnitus and vertigo, was first ascribed to herpetic lesion of the geniculate ganglion by Ramsay Hunt.[4] In the many papers which Hunt wrote on this subject, he described the postmortem changes in only 1 case, and in that the geniculate ganglion was not examined. We have found only one other histologic study of the "geniculate syndrome" in the literature, that of Maybaum and Druss,[5] who reported a case of periarteritis nodosa in which palsy of the face was present three months before death, and pain with blebs on the tympanic membrane, auricle and pinna six weeks before death. The cells of the geniculate ganglion were described as shrunken, pyknotic and, in some instances, disintegrated. The lesion shown in their illustration does not resemble that characteristic of herpes zoster. Our case 3, an instance of "occipitocollaris" and "auricular" herpes with palsy of the facial nerve, a variety of the syndrome recognized by Hunt,[4] is therefore of particular interest.

REPORT OF CASES

CASE 1.—H. T., a man aged 69, was admitted to the National Hospital for Nervous Diseases, Queen Square,

1. von Bärensprung, F. G. F.: (a) Die Gürtelkrankheit, Ann. d. Char.-Krankenh. zu Berlin 9:40-128, 1861; (b) Beiträge zur Kenntnis des Zoster, ibid. 10:96-104, 1862.

2. Head, H., and Campbell, A. W.: The Pathology of Herpes Zoster and Its Bearing on Sensory Localisation, Brain 23:353-523, 1900.

3. Lhermitte, J., and Nicolas: Les lésions spinales du zona: La myélite zostérienne, Rev. neurol. 1:361-364, 1924.

4. Hunt, J. R.: (a) Herpetic Inflammations of the Geniculate Ganglion: A New Syndrome and Its Complications, J. Nerv. & Ment. Dis. 34:73, 1907; (b) A Further Contribution to the Herpetic Inflammations of the Geniculate Ganglion, Am. J. M. Sc. 136:226, 1908; The Sensory System of the Facial Nerve and Its Symptomatology, J. Nerv. & Ment. Dis. 36:321-350, 1909; Herpetic Inflammations of the Geniculate, Auditory, Glossopharyngeal and Pneumogastric Ganglia, Arch. Int. Med. 5:631 (June) 1910.

5. Maybaum, J. L., and Druss, J. G.: Geniculate Ganglionitis (Hunt's Syndrome): Clinical Features and Histopathology, Arch. Otolaryng. 19:574-581 (May) 1934.
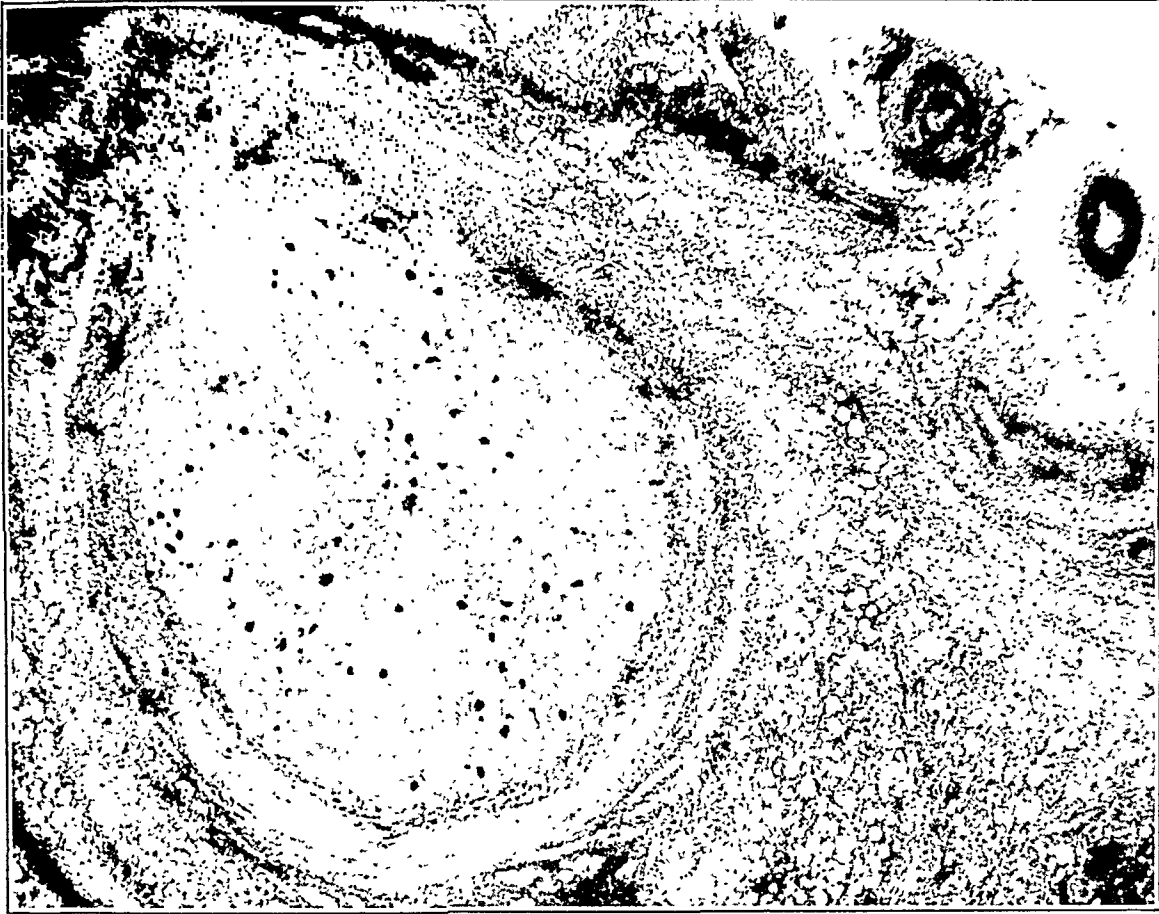
Fig. 1 (case 1).—Fifth dorsal root ganglion; Nissl stain. The capsule and periganglionic fat are infiltrated. The ganglion cells are visible only as pale "ghosts" in the necrotic area. The pigment of other cells remains as dark masses. In the right upper corner three small arteries are seen in section. The uppermost artery is occluded by an organized thrombus. The adventitia of the other arteries shows cellular reaction.

Fig. 2 (case 2).—Second cervical root ganglion; Bielschowsky method, counterstained with cresyl violet. Streaks of argentophil necrotic nerve fiber bundles cross the area of necrosis, where "ghost" cells and pigment are the sole remnants of the ganglion cells. The capsule and the peripheral parts of the ganglia are involved in a dense inflammatory reaction. Two arterioles are seen at the upper margin.

London, in September 1931, under the care of Dr. Hinds Howell, with the complaint of constant epigastric discomfort and shooting pains in the lower limbs of one year's duration. There had been deterioration of intellectual faculties over a similar period.

Examination.—He was talkative and emotional. Memory was defective. The pupils were small and fixed to light. Slight ptosis of the eyelids and some tremor of the tongue were noted. No defect in muscular power or in coordination was observed. The ankle jerks could not be obtained, but the knee and arm jerks were present and equal on the two sides. There were patchy areas of hypalgesia over the face and limbs and diminution of deep pain sensation in the achilles tendon and the testes. Sense of vibration was diminished in the lower limbs. On October 1 lumbar puncture revealed that the cerebro-

days after the last injection of the arsenical, a profuse hemorrhagic herpes zoster was found covering the region of the fifth and sixth dorsal cutaneous segments on the left side. No pain was associated with the eruption. A few days later there developed fever and obvious pneumonia, of which the patient died on December 11 (eleven days after the appearance of the eruption).

Anatomic Diagnosis.—The diagnoses were dementia paralytica and tabes dorsalis; herpes zoster, with inflammation of the fifth dorsal root ganglion on the left side, and terminal pneumonia.

Postmortem Examination (Dr. J. G. Greenfield).—Autopsy revealed pneumonia in the base on the left lung; edema of both lungs; notable cerebral atrophy, with much fluid in the meningeal spaces; some hemorrhagic fluid around the brain stem, and milky thicken-

Fig. 3 (case 1).—Fifth dorsal root ganglion; Gros-Bielschowsky method. Remnants of ganglion cells, one of which is vacuolated, with subcapsular whorls, and fine axis-cylinder fibrils at the margin of the necrotic area are shown. Dense lymphocytic infiltration is seen above. Below, and to the right, axis-cylinders extending into the necrotic zone end in knobs and clubs.

spinal fluid was under a pressure of 60 mm.; examination of the fluid revealed 26 lymphocytes per cubic millimeter, a total protein content of 55 mg. per hundred cubic centimeters, a weakly positive reaction for globulin, a colloidal gold curve of 4555555542 and a strongly positive Wassermann reaction. The Wassermann reaction of the blood was also strongly positive.

Course of Illness.—The patient was given mercury by inunction and iodides by mouth. Small elevations of temperature were induced on three occasions by the intravenous injection of bacterial vaccine made from the typhoid bacillus and the paratyphoid "A" and "B" bacilli U. S. P. A course of neoarsphenamine was also instituted, and the patient received 0.45, 0.45, 0.6 and 0.6 Gm. respectively at intervals of a week. On November 30, a few

ing of the spinal meninges. The cerebral meninges were slightly thickened. There was slight granular ependymitis.

Through the permission of Dr. J. G. Greenfield and Dr. Hinds Howell, one of us (Denny-Brown) was enabled to remove and examine the fifth dorsal root ganglion and the dorsal primary division of the fifth dorsal spinal nerve on the left side and a portion of the skin involved in the eruption.

Microscopic Examination.—Skin: There was considerable lymphocytic infiltration of the dermis and of the subcutaneous nerve branches under a vesicle.

Brain: The microglia of the cortex showed great overgrowth, with slight and scattered perivascular infiltration. There was loss of nerve cells in the frontal

cortex, with deposition of iron around the vessels and smaller amounts in the microglia. The spinal cord showed slight loss of myelin in the dorsal columns. This picture was consistent with the presence of dementia paralytica with slight tabetic changes.

Dorsal Primary Division of Intercostal Nerve Root: All parts of the nerve examined were infiltrated with lymphocytes and occasional plasma cells. There was complete degeneration of the axis-cylinders.

Fifth Dorsal Root Ganglion: The central portion of the dorsal root ganglion had undergone hemorrhagic necrosis. Normal ganglion cells were to be seen only in a narrow layer under the posterior aspect of the capsule of this ganglion. In many sections no stainable ganglion cells remained (fig. 1). The necrotic area was surrounded by a zone of inflammation, in which lymphocytes, plasma cells and a few polymorphonuclear leuko-

The largest artery and vein accompanying the spinal nerve were undamaged, but a small branch passing to the ganglion (fig. 1) contained an organized thrombus. In the adventitia of the vessel were many lymphocytes, plasma cells and histiocytes. Several smaller branches of this artery also were thrombosed. All vessels in the sheath of the ganglion were surrounded by lymphocytes.

The spinal nerve distal to the ganglion had many sound axis-cylinders, but the majority of these structures were in process of degeneration (fig. 4). The nerve was very cellular, owing to an increase in Schwann cells, histiocytes and plasma cells. In places small hemorrhages separated the fibers. The perineural sheath was separated from the nerve by a layer of lymphocytes and histiocytes, densely packed in places (fig. 5), and occasional hemorrhage. The gray ramus

Fig. 4 (case 1).—Peripheral nerve root about 3 cm. distal to the ganglion; Gros-Bielschowsky method, counterstained with cresyl violet. A small hemorrhage, degeneration of many nerve fibers, irregularity of the rest and cellularity of the perineurium (below) are shown.

cytes were densely packed (fig. 1). In the inner margin of this zone many degenerate forms were seen (fig. 3). Within this zone of infiltration the ghosts of ganglion cells were recognized by their pigment and faintly stained cytoplasmic outline. There was no recognizable capsule or satellite cells, and cellular interstitial elements were absent. In the inflammatory zone some ganglion cells showed shrinkage of the cell body and proliferation of subcapsular dendrites (fig. 3). In sections in which a margin of ganglion cells was stained by Nissl's method and by silver impregnation large clubs with a whorl of surrounding fibrils frequently occupied the capsule and vacuolated ganglion cells were evident (fig. 3). There had been hemorrhage into the necrotic area, and scattered lymphocytes and plasma cells permeated the sheath of the ganglion. The periganglionic fat also showed patchy inflammatory change.

communicans showed only slight cellular reaction, and its nonmedullated fibers appeared unaffected.

Dorsal Nerve Root: This portion of the nerve was completely degenerated in all sections. Only sparse argentophil remnants of axis-cylinders remained. The portion nearest the ganglion was completely necrotic, with hemorrhage within the root. More proximally, the root, as it passed through the meninges, was completely surrounded by a dense cuff of cellular exudate (fig. 6 A).

Ventral Nerve Root: There were many intact fine axis-cylinders, but in Bielschowsky preparations all the larger ones were either beaded or represented by chains of fragments (fig 6 B and C). Degeneration was more commonly encountered distally, where the root joined the peripheral portion of the nerve. The

sheath of the motor root as it passed the ganglion showed little cellular reaction.

Spinal Cord: In the gray matter of the fifth dorsal segment on the side of the affected ganglion the microglia was increased in both the posterior and the anterior horn, particularly in the region of Clarke's column. There was no cuffing of vessels. Some of the sensory nerve cells were replaced by clusters of microglia cells. An occasional anterior horn cell was in the process of phagocytosis (fig. 12 C), and others showed clumping Nissl substance in coarse granules around the periphery of the cell. No inclusion bodies were seen.

CASE 2.—*History.*—A man aged 74 attended the neurologic outpatient department of the Boston City Hospital because of a painful eruption over the left side of the chest, posteriorly and laterally. This was diag-

The sixth thoracic dorsal root ganglion on the left side was replaced by a cystlike cavity. The adjacent ganglia and the spinal cord were not remarkable.

Microscopic Examination.—Serial sections of the sixth thoracic dorsal root ganglion disclosed only the aforementioned cavity, surrounded by fibrous connective tissue. Neither inflammatory reaction nor hemorrhage suggested that this lesion was in any way related to the recent herpetic infection. The fifth and seventh ganglia on the left side were normal except for an occasional cluster of lymphocytes and a few empty capsules or capsules containing a few histiocytes. The great majority of dorsal root ganglion cells appeared undamaged. Most of the nerve fibers in the posterior root of the fifth thoracic segment had degenerated and were infiltrated with macrophages. In the leptomeninges and the posterior root there were many lymphocytes.

Fig. 5 (case 1).—Thoracic nerve at the origin of the dorsal primary division; Nissl stain. Clumps of lymphocytes appear among the nerve fibers, in the perineural space and in the epineurium.

nosed as shingles and treated with an antiseptic powder. The eruption cleared up during the next few days, but the pain continued.

Twenty-two days after the appearance of the eruption severe headache suddenly developed, and the patient became stuporous. He was taken immediately to the hospital, where examination disclosed a comatose condition with left flaccid hemiplegia. The blood pressure was 230 systolic and 140 diastolic. There were dry crusted lesions over the fifth or the sixth thoracic dermatome on the left side. The patient died the following day, twenty-three days after the first appearance of the herpetic eruption.

Anatomic Diagnoses.—The diagnosis was (1) cerebral hemorrhage and (2) herpes zoster with myelitis and ganglionitis (?) involving the sixth dorsal root ganglion on the left side.

Gross Examination.—There was massive hemorrhage in the basal ganglia of the right cerebral hemisphere.

In the left posterior horn of the gray matter at the fifth thoracic level nerve cells were undergoing destruction, there were large numbers of microglia cells and the small vessels were surrounded by lymphocytes. These changes were observed to a lesser degree in the left anterior horn at the same level but did not cross the midline to the right side. No inclusion bodies were observed in nerve cells of the spinal cord or the dorsal root ganglia.

No microscopic examination was made of the skin or the peripheral nerves.

CASE 3.—*History.*—A man aged 62 entered the Boston City Hospital Dec. 9, 1941, with the complaint of a painful rash over the head and neck of eight days' duration. The pain was severe, was limited to the right side of the face, occiput and neck and preceded the eruption by two or three days.

Prior to this illness the patient's health had been fairly good. Approximately ten years before admis-

sion he had a chronic cough and two years before he experienced periodic epigastric pain, which was relieved on institution of the Sippy diet.

Examination.—The temperature, pulse, respiratory rate and blood pressure were normal. The patient was well nourished and well developed; he appeared to be extremely uncomfortable but was not seriously ill. The skin in the right external auditory canal was swollen, red and desquamating. In the right occipital and post-auricular regions there was a vesicular eruption, as well as dry, scaling red papules which represented older lesions (fig. 7 *A*). The cervical lymph nodes on the

The Hinton reaction of the blood was negative. Chemical studies of the blood revealed 30 mg. of non-protein nitrogen and 5.85 Gm. of total protein per hundred cubic centimeters, with an icteric index of 5.

The stools were formed and brown and gave a positive reaction to the guaiac test. The sputum was negative for tubercle bacilli.

A roentgenogram of the chest revealed minimal fibroid tuberculosis of the apex of the right lung and emphysema.

Course.—On the third day in the hospital (December 12), the eleventh day of his illness, there developed
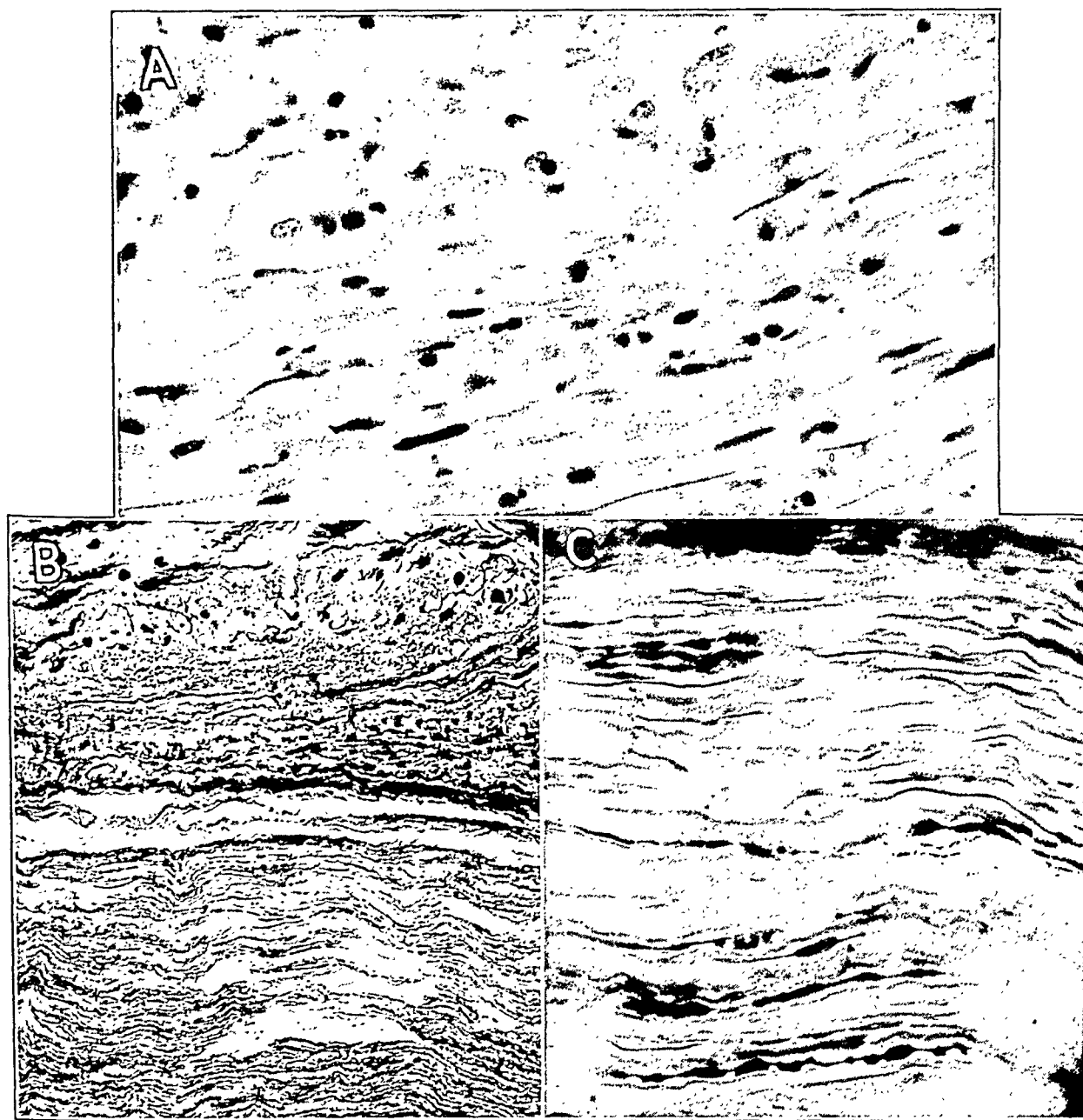
Fig. 6 (case 1).—Fifth dorsal root ganglion; Gros-Bielschowsky method. *A*, part of the meningeal course of the dorsal root, with meningeal reaction (above). *B*, ventral border of the ganglion and its capsule, above, in relation to the motor root, below. *C*, higher magnification of the area of independent degeneration of the ventral root shown in the center of *B*.

right side were enlarged and tender. The heart and lungs were not remarkable. The spleen was palpable 1.5 cm. below the costal margin. The liver was not palpable. Neurologic examination disclosed no abnormalities at this time.

Laboratory Data.—Examination of the urine showed only the slightest trace of albumin. The red blood cell count revealed 103 per cent hemoglobin, 4,900,000 red cells and 20,750 white cells, of which 75 per cent were polymorphonuclear leukocytes, 18 per cent lymphocytes and 7 per cent monocytes.

paralysis of the right side of the face, of lower motor neuron type (fig. 7 *B* and *C*), and the tongue deviated to the right. The paralysis was accompanied by a new eruption of vesicles over the posterior aspect of the right side of the head. Hearing was acute. There was impairment of pain and touch sensation over the second and third cervical segments on the right side, the area corresponding to that of the cutaneous eruption. All reflexes were within normal limits.

Examination of the cerebrospinal fluid (December 14) revealed that the pressure was normal; there were
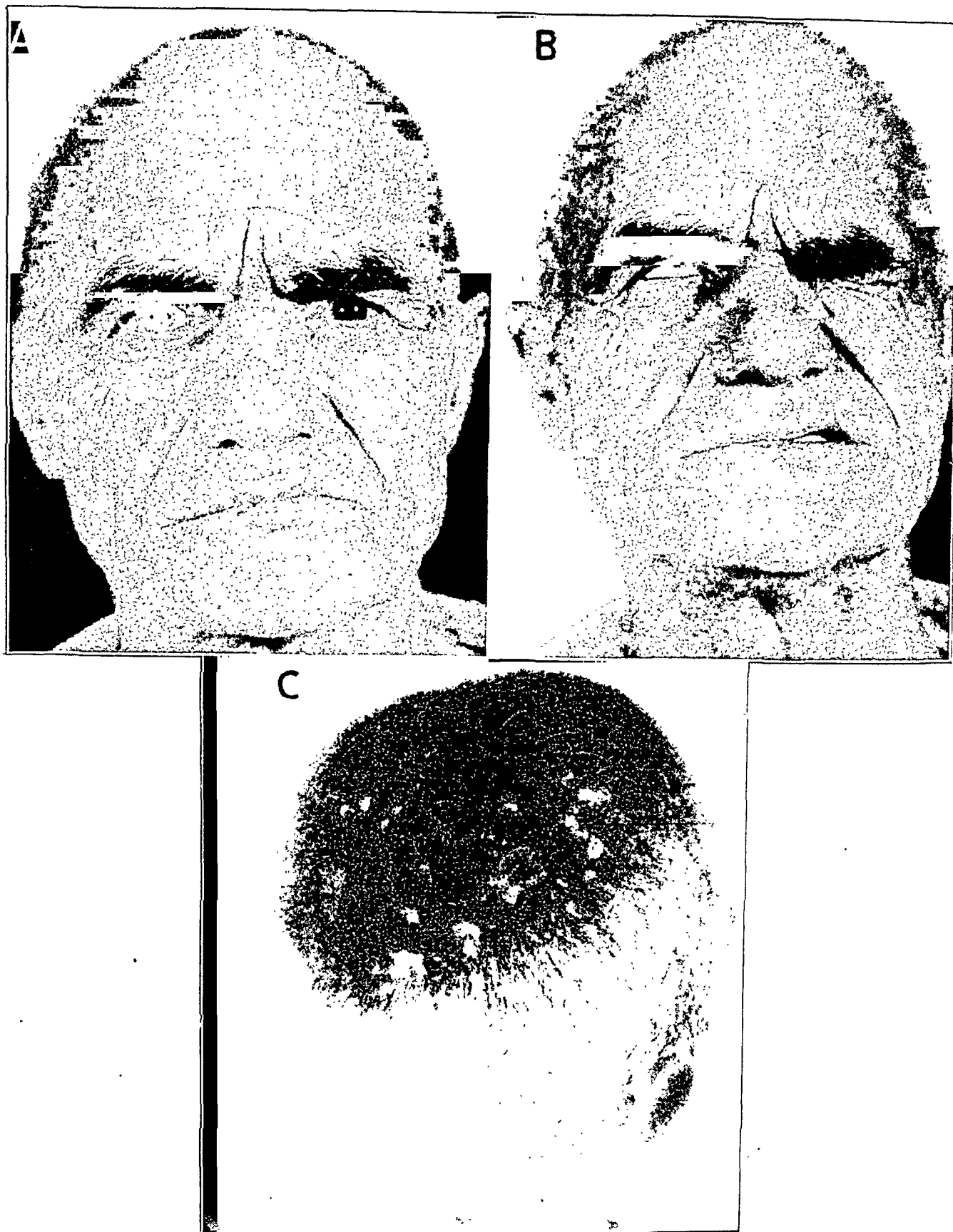
Fig. 7 (case 3).—Three views of the patient at the height of his illness, showing paralysis of the face and healing vesicles over the occiput.

89 lymphocytes per cubic millimeter and 35 mg. of protein, 52 mg. of sugar and 698 mg. of chlorides per hundred cubic centimeters; the colloidal gold reaction was 0112210000, and the Wassermann and Davies-Hinton reactions were negative.

During the next three weeks the facial palsy completely disappeared, and the pain gradually subsided. Most of the vesicles dried up, although on January 21 a small fresh cluster appeared immediately behind the right ear. Hypalgesia remained over the second and third cervical segments. The cell count of the cerebrospinal fluid gradually diminished to 47 lymphocytes per cubic millimeter on the twenty-second day of the illness, to 22 on the thirty-sixth day and, finally, to 15 on the fifty-third day after the onset of the herpes. The patient was discharged from the hospital but was readmitted one week later, on January 31, complaining of intermittent abdominal pain, occurring three or four

and to pass blood by rectum. The blood pressure fell, and he died on the third day in the hospital, or sixty-four days after the onset of herpes zoster, presumably of exsanguination.

Anatomic Diagnoses.—The diagnoses were herpes zoster with ganglionitis (second to third cervical ganglion) and myelitis; hemolytic icterus; peptic ulcer and gastrointestinal hemorrhage, possibly from the ulcer.

Postmortem Examination.—Autopsy was performed two and one-half hours after death. The peritoneal cavity contained 100 cc. of thin, fluid blood. The loops of the small bowel were distended and dark red; the large bowel appeared much darker than usual. There was no evidence of a perforated viscus and no exudate, palpable mesenteric nodes or fat necrosis. The right pleural cavity showed a few thin fibrous adhesions between the apex of the right lung and the anterior wall of the chest. The heart was normal in size, and the
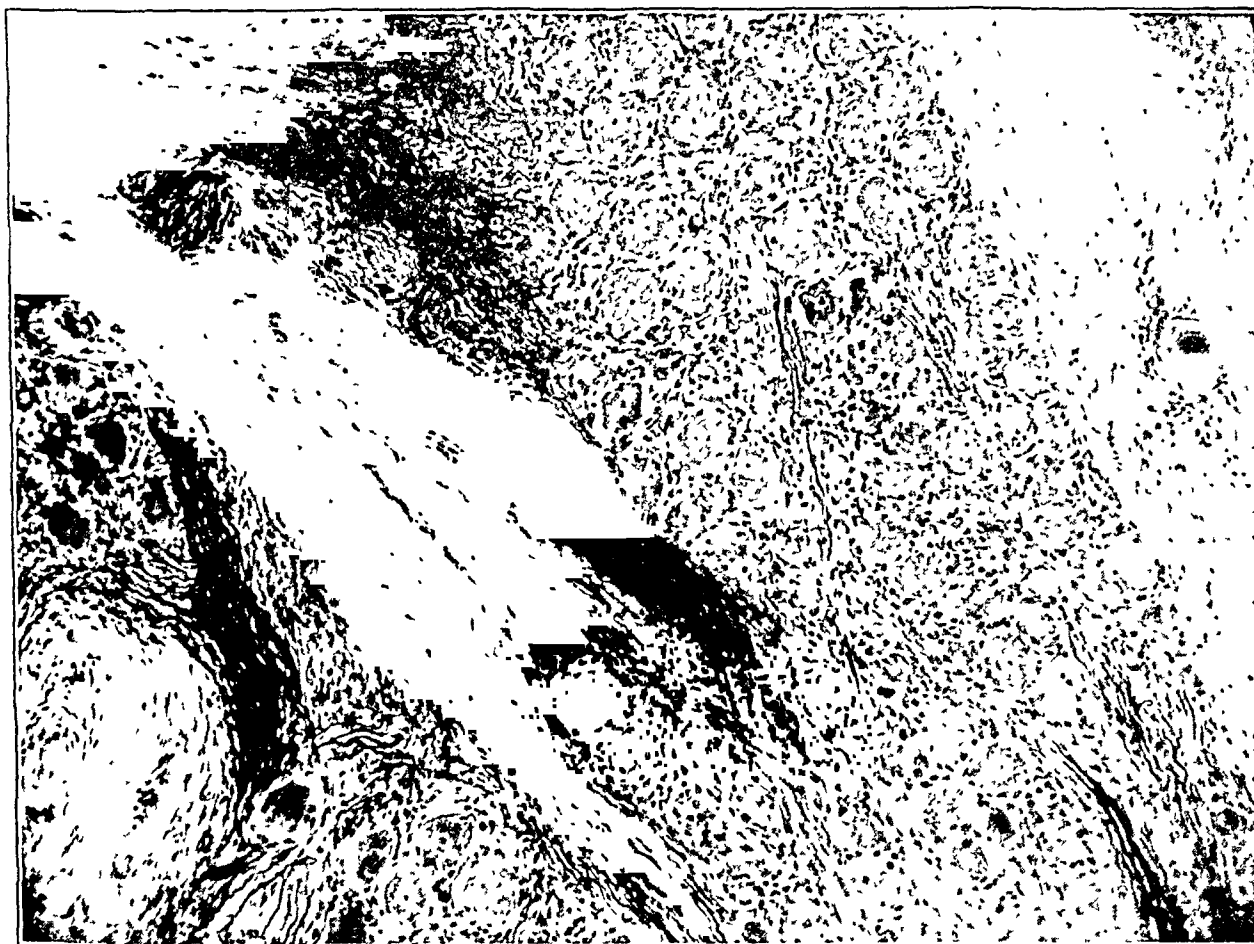
Fig. 8 (case 3).—Geniculate ganglion; Gros-Bielschowsky method, with cresyl violet. Normal ganglion cells and capsules and intraganglionic nerve fibers.

times a day, usually one hour after meals. On the day of his readmission to the hospital he vomited a large quantity of clotted blood and at about the same time evacuated a large amount of reddish black material from the bowel.

Second Examination.—The temperature was 97 F., the pulse rate 120 and the blood pressure 80 systolic. The patient appeared acutely ill. The skin and the mucous membranes were pale. There were pigmented and crusted lesions over the right side of the head and neck. The abdomen was tender.

Laboratory Data.—The stool gave a positive reaction to the guaiac test. Studies of the blood revealed 68 per cent hemoglobin and 67 mg. of nonprotein nitrogen per hundred cubic centimeters.

Course.—Despite administration of sedatives and 2,000 cc. of whole blood in several small transfusions over a period of three days, the patient continued to vomit

coronary arteries were relatively free from sclerosis. There was a firm fibrous scar in the apex of the right lung, but otherwise the lungs were crepitant throughout. The spleen weighed 290 Gm., and the capsule was tense, grayish purple and smooth. The cut surface showed firm, reddish purple tissue, with prominent trabeculations and increased consistence. The splenic artery and vein were patent. The esophagus was without varices or ulcer. A small ulcer, questionably healed, which measured 0.3 to 0.4 cm. in diameter, was observed on the lesser curvature of the stomach about 4 cm. from the pylorus. The ulcer did not extend more than 0.1 cm. into the mucosa, and no visible vessels were present in the base. The small bowel and the colon were filled with dark, fluid blood. The intestinal wall appeared viable, and dissection of the entire vascular system, both arterial and venous, revealed no thrombosis. It was impossible to determine whether the ulcer was the cause of the hemorrhage, but no other source was discovered.
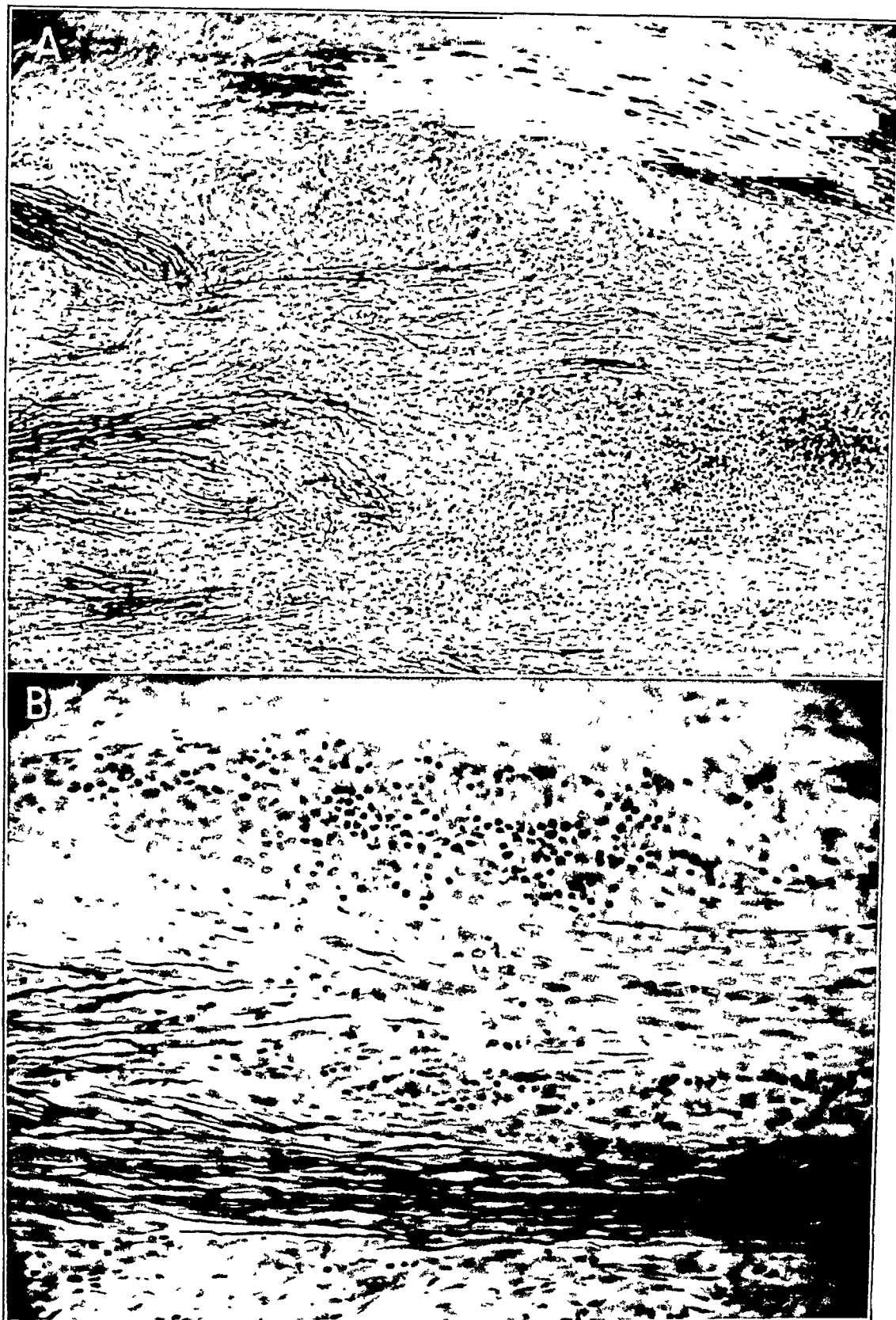
Fig. 9 (case 3).—*A,* focus of degeneration and regeneration, with cellular reaction in the motor fibers of the seventh nerve immediately proximal to the geniculate ganglion; Gros-Bielschowsky method, counterstained with cresyl violet. The sound fibers above are of the pars intermedia. The damaged nerve bundle below skirts the ganglion in its more distal course. *B,* a focus of inflammatory reaction and regeneration of axis-cylinders in the seventh nerve about 5 mm. distal to the ganglion. Note beading of the regenerating fibers, similar to that shown in *A.*

The liver weighed 1,380 Gm. The capsule was smooth and glistening, and the cut surface was finely lobulated and yellow-brown. The gallbladder and biliary system were normal. The kidneys were grossly normal. No lesions were observed in the brain or the spinal cord as examined in the fresh state.

together with the seventh nerve, from its meningeal course to just beyond the ganglion) and portions of nerves were stained with hematoxylin and eosin and with cresyl violet and by the Gros silver method for axis-cylinders and the Marchi method for products of myelin degeneration.
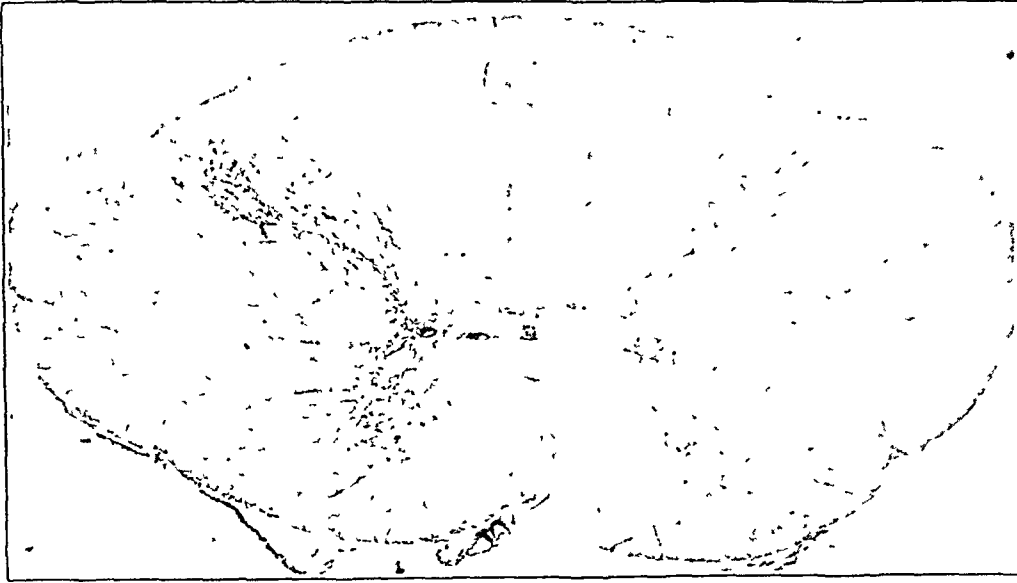
Fig. 10 (case 3).—Second cervical segment of the spinal cord; Nissl stain. Inflammatory reaction in the gray matter on the right side.
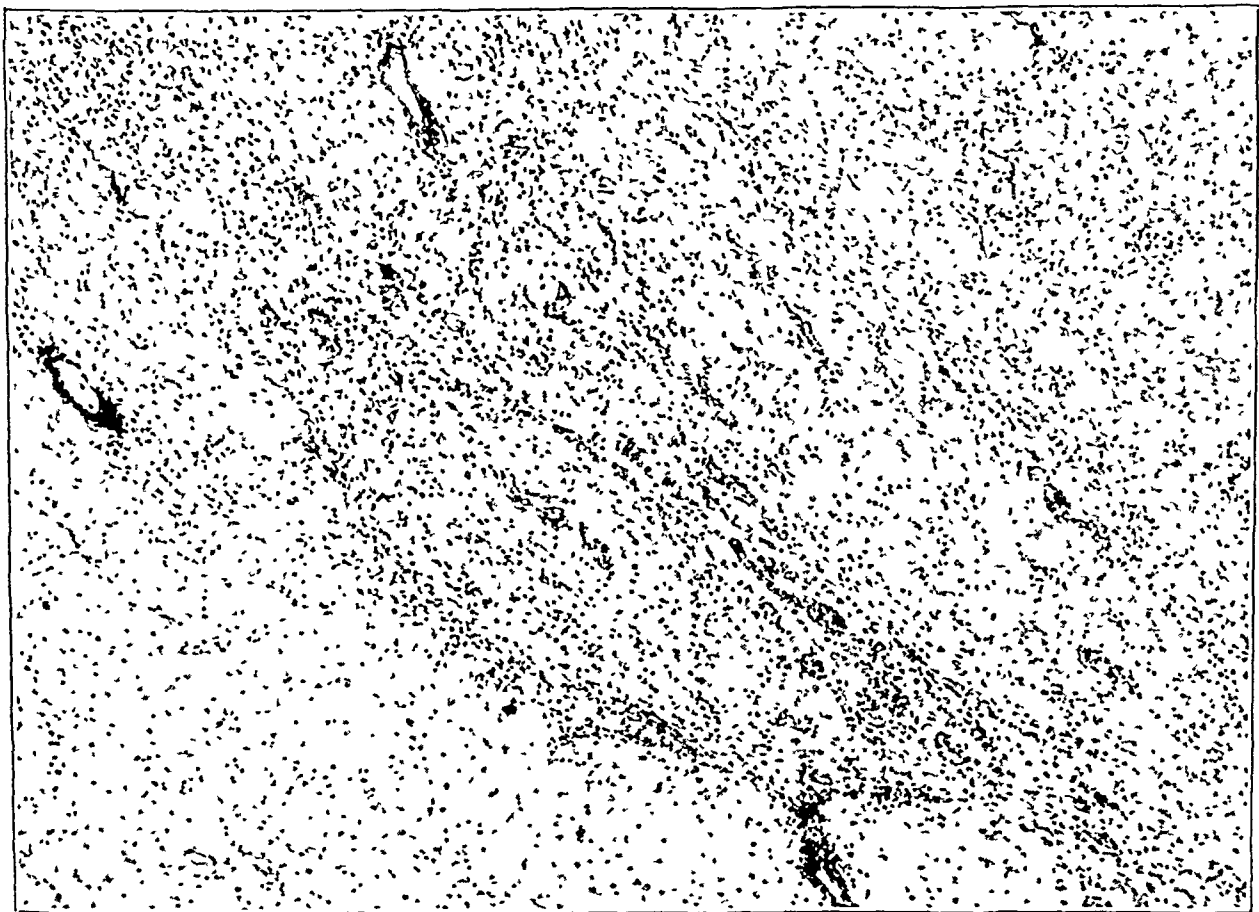
Fig. 11.—Higher magnification of part of the dorsal horn shown in figure 10.

Microscopic Examination.—The heart, esophagus, stomach, duodenum, jejunum, colon, pancreas, liver, adrenals, genitalia, aorta and hilar and aortic lymph nodes were normal. The venous sinuses of the spleen were widely patent and empty of red blood cells, and the endothelial lining cells were thickened. The splenic pulp contained large accumulations of red blood cells.

The brain, spinal cord, sensory ganglia, right geniculate ganglion (which was removed by dissection,

Seventh Nerve and Geniculate Ganglion: The geniculate ganglion contained a normal complement of cells, none of which appeared to have suffered any damage (fig. 8). There was no cellular infiltration.

Patchy infiltration with lymphocytes was observed throughout the course of the seventh nerve. In the intracranial portion of the nerve the cellular reaction was scattered and at no point intense. No certain evidence of damage to the nerve fibers was seen at this
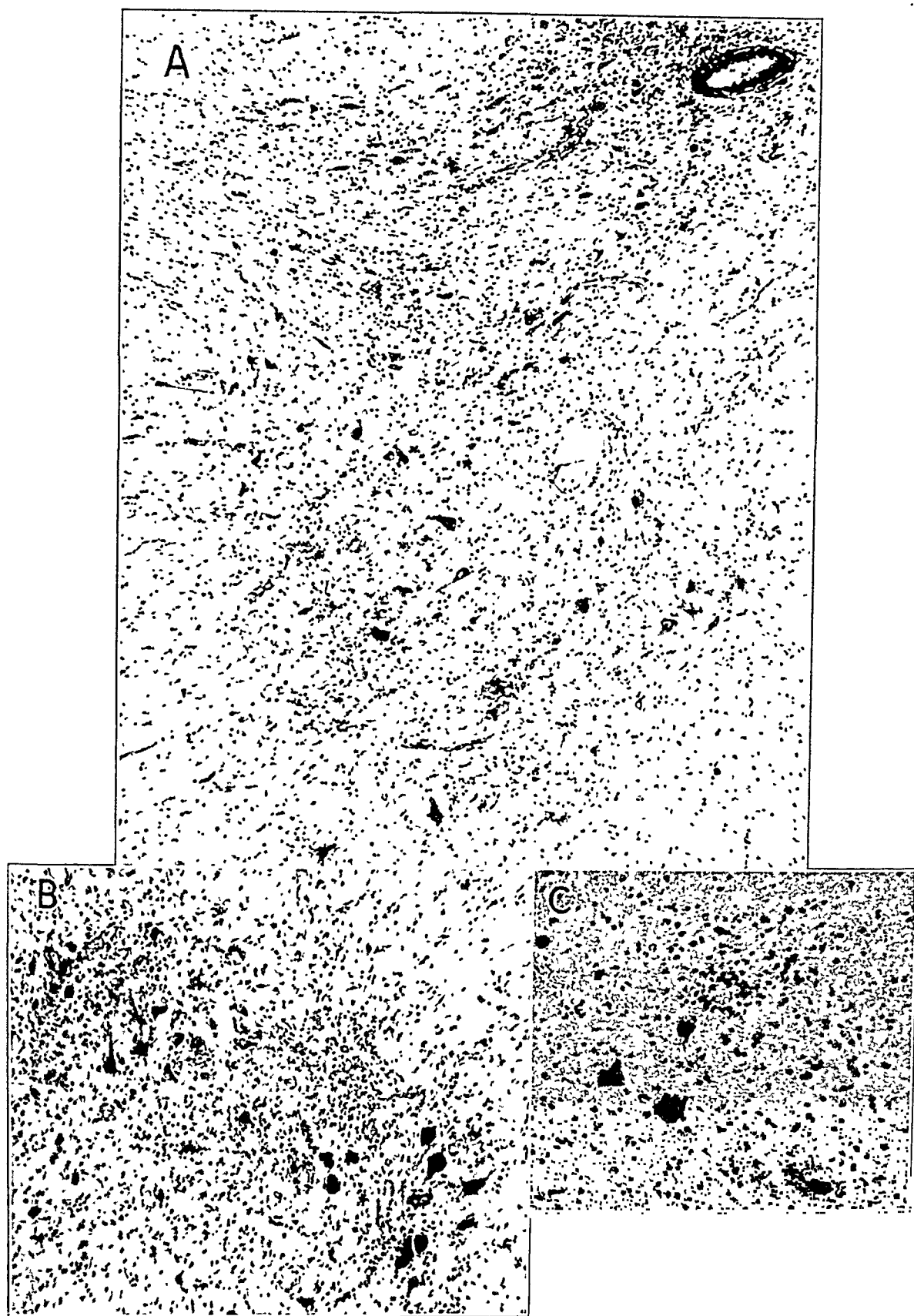
Fig. 12.—*A* (case 3), higher magnification of the ventral horn shown in figure 10, presenting perivascular infiltration in the upper right corner. *B* (case 3), ventral horn at the level of pyramidal decussation. There are proliferation of microglia and destruction of nerve cells. *C* (case 1), ventral horn of the fifth dorsal segment, showing neuronophagia and a small hemorrhage; iron hematoxylin and Van Gieson stain.

level. Immediately within the fallopian canal there was a dense patch of lymphocytic cells, with an occasional plasma cell. Such accumulations appeared at irregular intervals throughout the remainder of the course of the nerve. One focus lay just proximal to the geniculate ganglion (fig. 9 *A*) and another immediately distal (fig. 9 *B*), both clearly related to bundles of nerve fibers which did not enter the ganglion. The axis-cylinders related to such an accumulation were beaded and thinned, and a few had end bulbs. Nearer the internal auditory meatus an occasional single damaged axis-cylinder was visible.

Dorsal Root Ganglia (right side): Second cervical ganglion: The whole ganglion was virtually destroyed (fig. 2). The central portion was completely necrotic, faint "ghosts" of cell bodies being the only recognizable structures in sections stained with cresyl violet or hematoxylin and eosin. In Bielschowsky preparations necrotic remnants of axis-cylinders had still an argentophil property; these structures were seen as streaks crossing the necrotic zone in figure 2. In the necrotic region there were no viable cells, either interstitial or parenchymatous, nor were there any recognizable blood vessels.
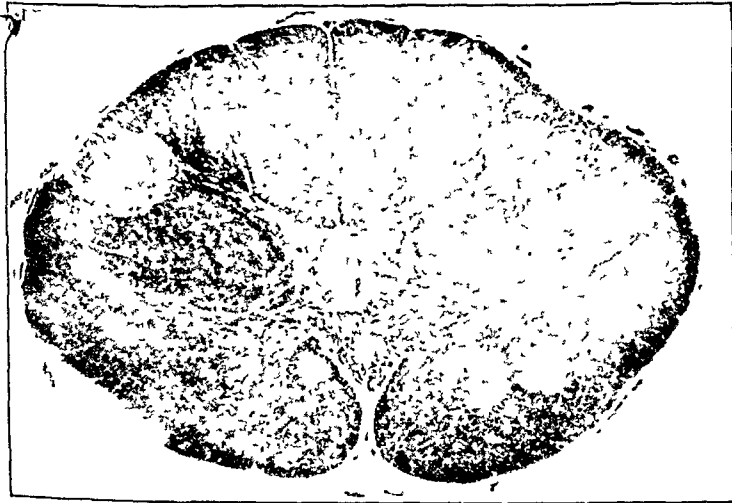
Fig. 13 (case 3).—Spinal cord at the pyramidal decussation, showing degeneration of myelin on the right side; Marchi stain.

The completely necrotic area was surrounded by a wide zone of dense lymphocytic infiltration extending to the capsule of the ganglion, which was also infiltrated. Proximally, the necrosis extended to the region of entry of the dorsal root, the root passing through the zone of lymphocytes as it entered the ganglion. Distally, the necrosis appeared to extend a distance of 1 to 2 mm. into the nerve as it issued from the ganglion. Beyond this cellular zone both the proximal and the distal portion of the dorsal root showed no remnants of axis-cylinders.

The portion of the ventral root which passed under the ganglion was diffusely infiltrated with lymphocytes. In its proximal part were many regenerating axis-cylinders, which became fewer as they were traced distally. In the region of fusion of the ventral and the dorsal root one or two axis-cylinders remained in each section.

The total destruction of the body of the dorsal root ganglion closely resembled infarct necrosis. The large vessels, both arterial and venous, which lay outside the ganglion were of normal appearance. The vessels in the sheath of the ganglion were "cuffed" with lymphocytes and showed endothelial proliferation, but contained red cells. There were no hemorrhages.

Third cervical ganglion: Most of the cells were intact. A few empty capsules and a few small collections of lymphocytes were present.

Fourth cervical ganglion: The ganglion was normal.

Fifth cervical ganglion: The ganglion was normal. The first cervical ganglion was not examined.

Posterior Roots in Their Meningeal Course: The first posterior cervical root was severely degenerated. The second posterior cervical root was completely degenerated, and no normal axis-cylinders could be seen. The root was infiltrated with lymphocytes; Schwann cells were increased in number and size, and histiocytes were abundant. The third, fourth and fifth posterior cervical roots were normal.

Spinal Cord: Level of pyramidal decussation: Here proliferation of microglia was conspicuous on the right side. Perivascular and meningeal infiltrates of lymphocytes were prominent. Many of the motor nerve cells in the supraspinal nucleus of the spinal accessory nerve on the right side were degenerated and surrounded by microglia cells (fig. 12 *B*).

First cervical level: Microglial proliferation was present in the posterior horn, with slight lymphocytic infiltration of the meninges. There was little change in the anterior horn at this level.

Second cervical level: There were large numbers of microglia cells in the posterior and anterior horns on the right side, lymphocytes in the perivascular spaces, clumping of Nissl substance in some nerve cells and necrosis and neuronophagia of others (figs. 11 and 12 *A*). The Marchi stain revealed degenerated nerve fibers medial to the posterior horn on the right side (fig. 13).

Third cervical level: A slight increase in microglia cells in the right posterior horn was the only alteration at this level.

Fourth and fifth cervical levels: Nothing abnormal was observed.

Brain Stem: Medulla: In the right lateral tegmental region were several small collections of microglial phagocytes. These were located between the spinal nucleus of the trigeminal nerve and the nucleus ambiguus. Two small vessels in this region, probably veins, were surrounded by a few lymphocytes, and similar cells infiltrated the leptomeninges on the right side. No definite damage to the nerve cells was noted.

Pons: Some of the nerve cells of the nucleus of the right seventh nerve were rounded and had undergone central chromatolysis (axonal reaction). No change in the hypoglossal or the cochlear nucleus was observed.

Cerebrum and Cerebellum: These areas were normal.

Skin: No inclusion bodies were observed. A section of a recent vesicle showed loss of epidermis and chronic inflammatory reaction in the dermis.

VIRUS STUDIES

Brain tissue was macerated with a pestle in a sterile mortar and mixed with enough isotonic solution of sodium chloride U. S. P. to make a suspension. One cubic centimeter of the mixture was placed on the scarified cornea of one eye in each of 2 rabbits. One rabbit received an intracerebral inoculation with 1 cc. of the mixture, and a similar amount was used to inoculate either the cerebrum or the peritoneal cavity of 3 mice. None of the animals exhibited systemic neurologic or cutaneous signs. No

corneal exudate was seen in the rabbit. After one month the animals were killed. No gross or microscopic lesions were seen. Examination of the corneas of the rabbits, after fixation in Zenker's solution and staining with phloxine and methylene blue, revealed no inclusion bodies.

COMMENT

Microscopic Changes.—The microscopic changes in the spinal ganglia constitute the most striking and distinctive pathologic feature of herpes zoster. In our cases and in those of many other authors, notably von Bärensprung[1] and Head and Campbell,[2] the spinal ganglion corresponding to the vesicular eruption had undergone partial or complete necrosis, with a varying amount of hemorrhage. In cases 1 and 3 in our series both parenchymatous and interstitial elements were destroyed so completely as to resemble "infarct necrosis," a fact suggesting vascular occlusion as the cause. In case 1 thrombosis of a main vessel to the ganglion was noted. Careful search in case 3 revealed no certain evidence of thrombosis or rupture of vessels. Head and Campbell[2] and Hedinger[6] drew attention to proliferation of the intima and cuffing of vessels, but they were unable to incriminate any single vessel in the ganglia which they examined. These changes were also present in 2 of our cases. Within the area of necrosis there were remnants of eosinophilic cells, or "ghost cells." These were surrounded by an intense inflammatory reaction and by a few still viable nerve cells. The connective tissue capsule of the ganglion was invaded by lymphocytes. Inconspicuous neuronic degeneration was seen in neighboring ganglia on the same side, when these were examined, a lesion also described by Head and Campbell.[2] It therefore appears unlikely that vascular thrombosis is primary in the disease, although the massive character of the focal necrotic lesion is strongly suggestive of vascular obstruction.

Hemorrhages into the ganglion, when present, appear to arise from small vessels in the necrotic region. In our case 1 and in a case cited by Head and Campbell[2] the hemorrhages were present in the peripheral nerve and in the cutaneous vesicles, as well as in the ganglion. In case 3 there was some extension of necrosis into the peripheral portion of the root. In case 1 the area of necrosis did not involve the whole ganglion, as Head and Campbell[2] also noted in some cases. In case 2 the ganglion appeared to be replaced by a cavity, along which ran the intact anterior root. The absence of inflam-

matory reaction in and around this cystlike cavity, only twenty-three days after the onset of the zoster, led us to question whether the spinal ganglion had escaped microscopic section. Complete destruction, however, has been noted in cases reported by Head and Campbell after a longer interval. In our case 3 the whole second cervical spinal ganglion was necrotic.

The changes in the dorsal nerve roots reflect the amount of damage in the ganglia. The change was a simple wallerian degeneration, with occasional patches of lymphocytic infiltration extending to the zone of entry of the root in the spinal cord. The isolated cellular changes in the adjacent ganglia were not usually accompanied by alteration of the dorsal roots.

All 3 cases in our series illustrate the extensive inflammatory changes in the central nervous system, first completely described by Lhermitte and Nicolas,[3] Wohlwill,[7] Faure-Beaulieu and Lhermitte[8] and others under the name "zoster myelitis." In the gray matter of the posterior and anterior horns of the spinal cord there was conspicuous proliferation of microglia cells, extending two or more segments from the one in which the cutaneous eruption occurred. This microglial reaction was accompanied by lymphocytic infiltration around veins and was strictly unilateral. A few plasma cells were noted in the infiltrations, as described by Lhermitte and Nicolas.[3] There was a mild meningeal infiltration, also of lymphocytes, over the affected segments of the cord, together with a corresponding reaction around the nerve roots; this focus was no doubt the origin of the persistent lymphocytosis in the spinal fluid. As previous investigators have noted, this inflammatory reaction is accompanied by scattered, but definite, damage to nerve cells, which in our cases was observed in the anterior horn, the substantia gelatinosa and Clarke's column on the affected side. Sections of cord stained by the Marchi method revealed the severe degeneration of the intramedullary portion of the dorsal root (fig. 13), medial to the dorsal horn, as described by a number of investigators. It will be noticed that the microglial reaction in corresponding Nissl sections (figs. 10 and 11) was distributed widely through the gray matter, and was not merely a secondary reaction to myelin degeneration. The microglial proliferation, the lymphocytic infiltration of the perivascular spaces and meninges and the necrosis and neuronophagia

6. Hedinger, E.: Beitrag zur Lehre vom Herpes zoster, Deutsche Ztschr. f. Nervenh. **24**:304-319, 1903.

7. Wohlwill, F.: Zur pathologischen Anatomie des Nervensystems vom Herpes zoster, Ztschr. f. d. ges. Neurol. u. Psychiat. **89**:170-212, 1924.

8. Faure-Beaulieu, M., and Lhermitte, J.: Les lésions médullaires du zona idiopathique: La myélite zostérienne, Rev. neurol. **1**:1250-1258, 1929.

of nerve cells combine to form a histopathologic picture which is characteristic of neurotropic virus infections. This disease is strictly a poliomyelitis; in none of our cases was there observed any demyelination, such as was described in 1 case by Lhermitte and Vermès,[9] the condition being complicated, however, by the presence of syphilis.

In cases 1 and 3 there was extensive degeneration of the anterior roots in their course past the corresponding necrotic ganglia. In case 3 the second cervical anterior root was completely degenerated at this point. The degree of degeneration of the motor roots in both cases exceeded the sparse necrosis of the anterior horn cells and appeared to indicate a true motor radiculitis.

This inflammatory reaction, so intense in the ganglia, spinal nerve roots and spinal cord, extended in milder degree into the peripheral nerves. A complete examination of peripheral nerves was not made in any of our cases, but we observed an intense inflammatory change in the intercostal nerve and in cutaneous filaments in case 1.

In summary, we affirm four histologic events which distinguish herpes zoster from other pathologic processes: 1. A ganglionitis marked by pannecrosis of all or part of the ganglion, with or without hemorrhage and surrounded by intense lymphocytic infiltration. This phenomenon was, in all published accounts and in our own cases, associated with the eruption of vesicles characteristic of the disease in the corresponding cutaneous segment. Wohlwill[7] alone claimed that inflammation of a nerve root or of a peripheral nerve can, without the necrotic ganglionitis, account for the zoster. 2. A poliomyelitis which closely resembles anterior poliomyelitis but is readily distinguished by its unilaterality, segmental localization and greater involvement of the posterior horn, posterior root and dorsal spinal ganglion. 3. A relatively mild, localized leptomeningitis, in which the cellular infiltrate is relatively slight and limited principally to the involved spinal segments and nerve roots. 4. True peripheral mononeuritis, seen not only in the nerves distal to the ganglion but in the anterior nerve root, both within the meninges and in the portion contiguous to the involved spinal ganglion. These pathologic changes are substratum for the neuralgic pains, the persistent pleocytosis and the local palsies which may attend and follow the zoster infection. There was no evidence of the location of fresh

disease corresponding to the fresh crop of vesicles in case 3 on the fifty-second day of the illness, but the extensive inflammatory changes and the persistent pleocytosis indicated continued activity of the pathogenic agent.

HERPES ZOSTER IN THE TERRITORY OF THE CRANIAL NERVES

The hypothesis of Hunt[4b] that the combination of a herpetic eruption in the external auditory meatus and palsy of the facial nerve is due to herpes of the geniculate ganglion has wide acceptance, in spite of the absence of pathologic proof. The hypothesis is attractive by reason of the explanation of the involvement of a motor nerve, a curiously localized area of cutaneous eruption and the frequency of association of these two lesions.

Prior to the first papers of Hunt,[4b] the sign of involvement of the pars intermedia and the geniculate ganglion associated with a lesion of the seventh nerve, according to the classic description by Erb,[10] had been a coexistent paralysis of the palate on the same side. The motor supply of the palatal muscles by the greater superficial petrosal nerve had already been questioned in 1907, but cases of palatal herpes and facial palsy, with or without auricular herpes, led Hunt[11] later to modify his hypothesis and include the soft palate as an alternative or additional area of sensory innervation by the geniculate ganglion. He also included a case in which the cutaneous eruption was limited to the posterior aspect of the pinna and the cleft between the ear and the mastoid process as illustrating an aberrant sensory distribution of the geniculate ganglion. Hunt provided an attractive argument for this variability in sensory supply of the geniculate ganglion based on the comparative anatomy of the seventh nerve and its branchial segment.

Whereas the hypothesis of "geniculate herpes" might explain the aforementioned strange sites of the eruption in association with palsy of the facial nerve, it encounters difficulty when the vesicles are found over the whole palate and within the nasal cavity on the affected side, as in the cases cited by Wakeley and Mulvaney,[12]

9. Lhermitte, J., and Vermès: Les lésions du système nerveux centrale dans la zona, Rev. neurol. **1**: 1231-1236, 1930.

10. Erb, W. H.: Diseases of the Peripheral Cerebrospinal Nerves, in Ziemssen, H.: Cyclopaedia of the Practice of Medicine, New York, W. Wood & Co., 1876, vol. 11.

11. Hunt, J. R.: The Sensory Field of the Facial Nerve: A Further Contribution to the Symptomatology of the Geniculate Ganglion, Brain **38**:418-446, 1915.

12. Wakeley, C. P. G., and Mulvaney, J. H.: A Rare Feature of the Ramsay Hunt Syndrome, with Some Observations on the Sensory System of the Seventh Nerve, Lancet **1**:746-749, 1939.

in which the lesions were attributed to involvement of the petrosal nerve, or when the eruption is localized to the anterior two thirds of the tongue without loss of taste, as in the case cited by Gowers.[13] Conversely, well established combinations of gasserian and geniculate zoster with meatal and tympanic eruption without palsy of the facial nerve, like that in the case described by O'Shea,[14] or gasserian and geniculate ganglionitis and facial palsy without auricular, postauricular or palatal eruption, which Spillane[15] and Wilson[16] reported as another variety of the geniculate syndrome, raise a doubt whether the motor division of the seventh nerve is damaged by an associated inflammation of the geniculate ganglion.

Kidd[17] questioned whether the geniculate ganglion supplies the cutaneous area of the meatus, the doubt being based chiefly on anatomic evidence that no such cutaneous area has been proved to exist in any animal group higher in the scale than cyclostomes. Sherrington[18] demonstrated that the cutaneous zone of the external auditory meatus, which retains sensation in the cat and monkey after section of the fifth cranial and the second cervical nerve root, is innervated by the vagus nerve in the cat. Convincing demonstration that the pars intermedia of the seventh nerve has nevertheless some sensory reference to the deep portion of the external auditory meatus was recently supplied by Furlow,[19] who stimulated this nerve in its meningeal course at open operation in a conscious patient and thereby duplicated the pain of meatal neuralgia. No definite area of loss of sensation was demonstrated after section of the nerve. In the same manner, Reichert[20] demonstrated that the glossopharyngeal nerve supplies the same region, without loss of sensation in the area on section. In both these cases paroxysmal neuralgia had occurred in the area of meatal innervation and was relieved by section of the appropriate nerve. The possibility of some overlapping sensory innervation of the tympanic portion of the meatus by all three nerves, the pars intermedia, the glossopharyngeal and the vagus, must therefore be conceded. Of these, the vagus nerve, through the branch called the nerve of Jacobsen, has apparently the largest share.

In case 3 the geniculate ganglion was entirely unaffected, in spite of cutaneous eruption in the meatus and, later, postauricular eruption of the type also attributed by Hunt to involvement of the geniculate ganglion. An explanation for the various areas of eruption is to be sought in the involvement of other ganglia. We regret that the ganglia of the vagus and glossopharyngeal nerves were not examined in our case, but from the occurrence of a circumscribed microglial reaction in the lateral portion of the medulla, we suspect that one of these ganglia was involved. The extremely localized areas of cutaneous eruption which can occur within the territory of the fifth nerve (nasal cavity; tongue) and the patchy involvement of ganglion cells in ganglia other than the one which is the chief focus of necrosis both give warning, however, that narrow limitation of the cutaneous eruption may mean only a localized, partial lesion of the gasserian ganglion. Nor is it certain that herpes zoster does not on occasion affect the geniculate ganglion. If geniculate herpes is to be established as a pathologic entity, careful microscopic examination of all the cranial nerves and ganglia in a series of cases will be necessary, a study advocated by Mills[21] in an early criticism of the "geniculate syndrome."

Our case 3 indicates clearly, however, that damage to the seventh nerve can occur in the course of herpes zoster by the mechanism of an independent motor neuritis not directly related to inflammation of any ganglion. This observation at once removes one necessity for Hunt's hypothesis, namely, the mechanism of damage to the seventh nerve, and provides an explanation of the occasional involvement of oculomotor nerves in the course of ophthalmic herpes.

SUMMARY AND CONCLUSION

The dorsal root ganglion corresponding to the area of herpetic eruption was the site of inflammatory necrosis in 2 cases of herpes zoster,

13. Gowers, W. R.: A Manual of Diseases of the Nervous System, ed. 2, Philadelphia, P. Blakiston's Son & Co., 1900, vol. 2, p. 241.

14. O'Shea, H. V.: Otitis Herpes Zoster, Practitioner **125**:741-748, 1930.

15. Spillane, J. D.: Bell's Palsy and Herpes Zoster, Brit. M. J. **1**:236-237, 1941.

16. Wilson, S. A. K.: Neurology, Baltimore, Williams & Wilkins Company, 1940, vol. 1, p. 678.

17. Kidd, L. J.: The Alleged Sensory Cutaneous Zone of the Facial Nerve of Man, Rev. Neurol. & Psychiat. **12**:393-410, 1914.

18. Sherrington, C. S.: Reflexes Elicitable in the Cat from Pinna, Vibrissae and Jaws, J. Physiol. **51**:404-431, 1917.

19. Furlow, L. T.: Tic Douloureux of the Nervus Intermedius (So-Called Idiopathic Geniculate Neuralgia), J. A. M. A. **119**:255-259 (May 16) 1942.

20. Reichert, F. L.: Tympanic Plexus Neuralgia, J. A. M. A. **100**:1744-1746 (June 3) 1933.

21. Mills, C. K.: The Sensory Functions Attributed to the Seventh Nerve, J. Nerv. & Ment. Dis. **37**:273-284 and 355-379, 1910.

and in a third case a cyst replaced the ganglion. In all 3 cases there were degeneration of the related motor and sensory roots, severe neuritis, unilateral segmental poliomyelitis and localized leptomeningitis. These pathologic changes constitute a distinct neuropathologic syndrome and provide an explanation for such commonly observed clinical events as neuralgia, motor palsies and pleocytosis.

The third case in our series, one of auricular and occipital herpes with palsy of the facial nerve, is of considerable interest because of the rarity of cases with autopsy. Here a typical necrotizing ganglionitis (second cervical ganglion) and motor neuritis of the facial nerve without damage to the geniculate ganglion were observed.

It is concluded that the phenomena of herpes zoster require more than the ganglionic lesion for their explanation, but depend in part on a poliomyelitis and motor neuritis. Application of these deductions to the syndrome described by Ramsay Hunt allows an explanation of the facial palsy occurring in the course of cranial herpes zoster without implication of the geniculate ganglion.

Analysis reveals that the evidence for geniculate ganglionitis in the "Ramsay Hunt syndrome" is invalid. It is possible that some of the various herpes zoster syndromes with palsy of the facial nerve depend on the concurrent involvement of two or more cranial nerves.

Neurological Unit, Boston City Hospital.

ELECTRONARCOSIS IN ANIMALS AND IN MAN

J. P. FROSTIG, M.D.; A. van HARREVELD, M.D.; S. REZNICK, M.D.;
D. B. TYLER,* Ph.D., and C. A. G. WIERSMA, Ph.D.

PASADENA, CALIF.

In the beginning of this century Leduc [1] produced a narcosis-like state in rabbits and in dogs by applying a unidirectional pulse current to the central nervous system. The cathode was placed on the head and the anode on the sacrum. "Electronarcosis" was started by application of a relatively high current, which caused strong contractions of the body musculature. The animal fell on its side; respiration stopped, and the bladder, and sometimes the rectum, were emptied. After a few seconds the current was decreased to a level at which respiration returned. The animal remained motionless as long as the current was maintained (1 to 4 milliamperes, as measured with a ballistic galvanometer) and could not be aroused even by strong stimuli. Electronarcosis could be maintained for an indefinite time. As soon as the current was interrupted, the animal awoke, without any apparent ill effects.

Leduc's observations have been confirmed by several investigators (von Neergard,[2] Zimmermann [3]). Some authors, however, observed strong excitatory phenomena during the application of a pulsating current to the central nervous system (Sack and Koch,[4] Koch and Sack,[5] Samssonow [6]).

Leduc, assisted by Malherbe and Rouxeau,[7] tried out the procedure on himself. The pulsating current was slowly increased. At the beginning of the application unpleasant sensations were experienced at the site of the electrodes. These sensations ceased on further increase of the current. The first sign of central involvement was his inability to speak; soon afterward he was unable to move, although he still remained conscious. During the application of the strongest current that Malherbe and Rouxeau dared to give, Leduc heard what was said, but perception was "dreamlike" and painful stimuli were felt as though they were applied to an extremity deeply asleep. A few years later Tuffier and Jardry [8] and Leclerc [9] used electronarcosis in a few clinical operations on animals and on man, apparently with some success.

It has been shown that there is a fundamental difference between the mechanism of electronarcosis and that of chemical narcosis (van Harreveld, Plesset and Wiersma [10]), since the narcotic action of the electric current depends on its stimulating effect. This difference is well illustrated by the fact that the metabolism of the brain, which is reduced in chemical narcosis, remains practically unchanged during electronarcosis (van Harreveld, Tyler and Wiersma [11]). In view of the work of Leduc, answers were

1. Leduc, S.: Production du sommeil et de l'anesthésie générale et locale par les courants électriques, Compt. rend. Acad. de Paris **135**:199-200 and 878-879, 1902; Ann. d'électrobiol. **5**:526-527, 1902; Production du sommeil et de l'anesthésie générale et locale par les courants intermittents de basse tension, Arch. d'électric. méd. **10**:617-621, 1902; L'électrisation cérébrale, ibid. **11**:403-411, 1903; La narcose électrique, Ztschr. f. Elektrother. **5**:374-381 and 403-410, 1903; Der elektrische Schlaf, Arch. phys. Med. u. med. Techn. **5**:3-15, 1911.

2. von Neergard, K.: Experimentelle Untersuchungen zur Elektronarkose, Arch. f. klin. Chir. **122**:100-150 1922.

3. Zimmermann, J.: Untersuchungen über die Anwendbarkeit der elektrischen Betäubung nach Leduc bei chirurgischen Eingriffen an Hunden, München. tierärztl. Wchnschr. **80**:121-124, 141-145 and 155-159, 1929.

4. Sack, G., and Koch, H.: Zur Frage der sogenannten Elektronarkose durch wiederholte Gleichstromstösse, Ztschr. f. d. ges. exper. Med. **90**:349-364, 1933.

5. Koch, H., and Sack, G.: Elektronarkoseversuch: Untersuchungen über die Wirkung periodischer rechtwinkliger Gleichstromstösse, Ztschr. f. d. ges. exper. Med. **90**:365-377, 1933.

6. Samssonow, N.: Beitrag zum Studium der Elektronarkose, Arch. f. d. ges. Physiol. **232**:554-558, 1933.

7. Leduc, S.; Malherbe, A., and Rouxeau, A.: Production de l'inhibition cérébrale chez l'homme par les courants électriques, Compt. rend. Soc. de biol. **54**:1297-1299, 1902.

8. Tuffier and Jardry: Les applications du sommeil électrique a la chirurgie expérimentale, Presse méd. **15**:259, 1907.

9. Leclerc, G.: L'anesthésie électrique chez l'homme, Cong. franç. de chir. **23**:665, 1910.

10. van Harreveld, A.; Plesset, M. S., and Wiersma, C. A. G.: The Relation Between the Physical Properties of Electric Currents and Their Electronarcotic Action, Am. J. Physiol. **137**:39-46, 1942.

11. van Harreveld, A.; Tyler, D. B., and Wiersma, C. A. G.: Brain Metabolism During Electronarcosis, Am. J. Physiol. **139**:171, 1943.

sought to the following questions: Can a method be devised by which the human brain can be exposed to the action of an electric current for periods longer than a fraction of a second, as used in electric shock? What are the symptoms caused by this procedure? Is such a method compatible with the safety of the patient? In order to obtain an answer to these questions, first animals and subsequently human subjects were exposed to the prolonged action of the current applied to the brain.

CHOICE OF CURRENT AND APPARATUS

Leduc expressed the opinion that the only current capable of producing electronarcosis was a unidirectional pulsating current with a frequency of about 100 per second and a pulse duration of one millisecond. It was found later, however, that a 50 cycle, sinusoidal alternating current also is suitable for induction of electronarcosis (van Harreveld and Kok[12]). Recently it has become evident that any current capable of stimulating the central nervous system can be used to produce electronarcosis (van Harreveld, Plesset and Wiersma[10]). Any variation in current of sufficient duration and slope will cause such a stimulation. Since the central nervous system must be stimulated for the entire duration of electronarcosis, these variations in current must be repeated with suitable frequency. Thus it is not surprising that pulsating, as well as alternating, current can cause electronarcosis and that direct current, which has hardly any stimulating properties except during the onset, is less suitable for this purpose (Tschagowetz[13]; Silver[14] van Harreveld, Plesset and Wiersma[10]). Since alternating current is the most readily available, this form of electricity has been used in all the present experiments. Because of the difference in the local supplies of current in Pasadena and in Patton, the animal experiments were carried out with a 60 cycle current and the experiments on human subjects with a 50 cycle current. Experiments on dogs have shown that the symptoms of electronarcosis produced by currents of these two frequencies are the same.

In a large number of the experiments on dogs and in all applications of current to human subjects an apparatus based on the principle of current control described by Plesset[15] was used. This apparatus automatically compensates for moderate changes in resistance in the subject's circuit. Changes in the resistance of the electrode contacts, which are hardly avoidable in a restive subject, are therefore of no consequence, since the current passing through the head remains constant. The maximum output of this apparatus is 250 milliamperes.

In the animal experiments electrodes, 2 cm. in diameter, were placed on both sides of the skull directly behind the eyes. With the human subjects square electrodes, measuring 5 by 5 cm., were used. Except in the investigations on the influence of placement of electrodes, the electrodes were placed on the temples. To assure a good contact an electrode paste was applied between the electrodes and the skin. The electrodes were kept in place by bandages.

In all animal experiments the pulse rate and the respiratory rate were obtained in the usual way. The blood pressure was determined in some experiments by connecting a large artery (the femoral or the carotid) with a recording mercury manometer. In the work with patients the blood pressure was measured by the auscultatory method in one of the arms, and the heart rate was determined by means of a stethoscope taped over the region of the apex beat. These determinations were made at alternate half-minute intervals for the entire duration of the electronarcosis and for some time afterward.

OBSERVATIONS

Various methods of induction of electronarcosis were studied, first in dogs and later in human subjects. In the latter the influence of various placements of the electrodes was studied. Since with respect to the safety of the procedure the reactions of the circulatory apparatus are of primary importance, the influence of electronarcosis on the heart and blood vessels will be described in a special section. In addition, the results of studies on the chemical constituents and the morphologic features of the blood will be presented.

The observations were made on adult dogs of various kinds, sizes and ages and on patients of both sexes with a history of dementia precox of at least four years' standing. The age of the patients varied from 20 to 45 years.

Symptoms of Electronarcosis in Dogs.—The following standard procedure for the production of electronarcosis was employed: A relatively strong current (e. g., 300 milliamperes of a 60 cycle alternating current) was applied for thirty seconds, after which the current was decreased in strength (e. g., to 50 milliamperes).

Immediately on application of the strong current, the legs flexed actively, and the standing animal fell. The period of flexion was very short, and for the next few seconds the legs were without tone. After the current had been applied for five to ten seconds, however, a strong

12. van Harreveld, A., and Kok, D. J.: Ueber Elektronarkose mittels sinusoidalen Wechselstromes, Arch. néerl. de physiol. **19**:24-57, 1934.

13. Tschagowetz, W.: Ueber die Veränderung der reflektorischen Erregbarkeit des intermittierenden galvanischen Stromes auf das Zentralnervensystem, Arch. f. d. ges. Physiol. **146**:567-577, 1912.

14. Silver, M. L.: Electrical Anesthesia in Rats, Proc. Soc. Exper. Biol. & Med. **41**:650-651, 1939.

15. Plesset, M. S.: Current Control in Electroshock Therapy, Proc. Soc. Exper. Biol. & Med. **49**:530-532. 1942.

extensor spasm developed in the legs. In addition there was opisthotonos. The position of the animal at this time resembled closely that of pronounced decerebrate rigidity. There was complete respiratory arrest. This state remained unchanged as long as the strong current was applied. In most experiments urine was passed during this period, and sometimes a bowel movement occurred. Immediately on application of the current the heart was arrested for a few seconds; it then started to beat again, beginning at a very low rate.

The decrease in the strength of the current after thirty seconds resulted in relaxation of the extensor spasm and the appearance, within a few seconds, of clonic twitches, which receded spontaneously in a short time (five to ten seconds). Sometimes, instead of clonic twitches, coarse shaking was observed.

If the current had been decreased sufficiently, the first respiratory movement occurred fifty to seventy seconds after the beginning of the experiment. If the decrease in current was insufficient, the return of respiration was delayed, but breathing could be established by further diminishing the current. At first respiration was gasping and infrequent, but soon breathing became more normal. The intensity of current at which adequate respiration was possible depended on the type of current used and the individual reaction of the animal, and probably on the placement of the electrodes. Usually 40 to 70 milliamperes of a 60 cycle alternating current was compatible with adequate respiration.

After regular respiration had been established, the animal lay quietly and without tone in the muscles, although sporadically light clonic twitches might occur. If respiration at this time was still inadequate, improvement could be achieved by a slight decrease in the strength of the current. The highest level of current which was compatible with adequate respiration has been designated the narcosis level.

During the subsequent course of application of the current one of two syndromes might develop; these have been distinguished as the narcotic and the kinetic type of electronarcosis. The narcotic type is a continuation of the state just described. In this state the animal lay quietly, breathing slowly and deeply. Respiration might be somewhat labored and noisy. Von Neergard [2] found that this stertorous breathing was due to contraction of the vocal cords, which impeded the passage of the air. After tracheotomy respiration was perfectly free. In this form of electronarcosis the heart

rate was low, about half the normal rate. The animal showed no spontaneous activity except for respiratory movements, and in some cases occasional clonic twitches. The front legs were usually extended and the hindlegs semiflexed. This is the typical position of dogs when no pronounced tone prevails. Positive and negative supporting reactions (Rademaker [16]) were present when the legs were placed in the proper positions. In particular, the front legs when brought into the position for standing became more or less rigid. Nevertheless, when the animal was placed on its legs, it was not able to stand. Except for the positive supporting reaction, no appreciable tone was present in the legs. The head was usually dorsally extended, and the eyes were tightly closed; these symptoms may be ascribed to direct stimulation of the muscles involved. Tendon reflexes, such as the knee jerk, were usually of about normal excitability. No righting reflexes could be elicited. Pinching or pricking the skin produced no reaction. The pupils were usually in middilatation, and the pupillary reaction to light, if present, was sluggish. Pressure on the eyeballs through the closed eyelids was often without effect but sometimes caused defecation or irregularities of respiration. Many dogs from time to time had a spontaneous bowel movement. Once this narcotic type of electronarcosis was established, it could almost invariably be maintained for hours.

Increase of the current beyond the value necessary to maintain this state caused an extensor tone in the legs which was independent of the position of the legs. Respiration became more difficult, owing to contraction of the glottis, and was sometimes inadequate. In most animals this occurred when the current was increased about 20 milliamperes above the narcosis level. Sudden increases in the current might arrest respiration, whereas the same increase extended over several minutes might not produce any notable change in the rate of breathing.

As the current was decreased below the level at which the narcotic effect of electronarcosis was obtained, the supporting reaction became stronger and stronger until the animal, when placed on its legs, remained in a standing position. Even in this state there was no return of spontaneous movements, of righting reflexes or of reactions to cutaneous stimuli. When the legs were placed in abnormal positions, no corrective movements were made. These cataleptic phenomena have been observed before on application

16. Rademaker, G. G. J.: Das Stehen, Berlin, Julius Springer, 1931.

of current to the head (Keller,[17] van Harreveld and Kok [18]). If during this cataleptic state the current was slowly increased, a reversal of the phenomena could be obtained, and the narcotic state could be reestablished. The difference in currents producing these two states was about 20 milliamperes. When during prolonged electronarcosis the current was kept at the same level, the narcotic state changed slowly into the cataleptic state. Therefore, to maintain a constant depth of electronarcosis for long periods the narcotizing current must be gradually increased.

When the current was turned off during a period of electronarcosis of the narcotic type, the animal recovered in the course of a few minutes, usually passing through a transitional period of catalepsy.

The second, or kinetic, type of electronarcosis was characterized by frequent attempts of the animal to right itself, movements which were often ataxic and usually unsuccessful. These attempts might develop into violent and disordered hyperkinesis of the head and extremities, which was often preceded or accompanied by yelping or whining. Between righting attempts the animal was quiet, but righting and hyperkinesis could be induced by certain stimuli, the most effective of which was pressure on the eyeball. Also effective was moving the animal, inducing stimulation of the vestibular apparatus, and perhaps other sensory systems. In some cases cutaneous stimuli were effective. The heart and respiratory rates were higher in this type of electronarcosis than in the narcotic type, and as a rule were higher than normal. When the current was decreased, the placing reaction could often be elicited. Increase of the current produced pronounced extensor tone in the legs, and the hyperkinetic symptoms might become aggravated. Once the hyperkinetic type of electronarcosis became pronounced, neither increase nor decrease in the current was effective in changing it into the narcotic type. If the current was cut during the hyperkinetic type of narcosis, immediate recovery without cataleptic symptoms followed. After awakening the animal often panted and showed excitement for several minutes.

The hyperkinetic type of electronarcosis was less frequent than the narcotic type. Often some kinetic symptoms, such as an occasional weak attempt of the animal to right itself, temporary

yelping or movements on pressure on the eyeball, were observed during electronarcosis of the narcotic type. The type of electronarcosis produced is largely an individual reaction of the animal. However, in the course of a long series of inductions of electronarcosis in the same animal, kinetic symptoms may appear or, if present at first, may become aggravated. Occasionally hyperkinetic symptoms may become increasingly apparent in the course of a prolonged period of narcosis.

Several variations in the procedure were investigated; the results of the more important ones may be described. It was attempted to produce electronarcosis by slowly increasing the current to the narcosis level instead of starting with an initial strong current of thirty seconds' duration and subsequently decreasing it to the narcosis level. In these experiments only dogs in which the standard procedure caused electronarcosis of the narcotic type were used. In most animals this method of application of current resulted in a violent hyperkinetic type of electronarcosis, and only in a few could a narcotic type be obtained. The flexion and the secondary extensor spasm observed during application of the strong initial current in the standard procedure were absent with this method. In the few experiments in which a narcotic type of electronarcosis was obtained with this procedure, the animal toppled over slowly, without any hyperkinetic symptoms. In another series of experiments, shortening of the duration of the strong initial current resulted in a greater frequency of hyperkinetic symptoms than was encountered with the standard procedure. The same effect was noted when the strength of the initial current was materially decreased. In the latter experiments a slow, late development of the extensor spasm was observed.

Symptoms of Electronarcosis in Man.—More than 100 electronarcoses were induced in a series of 9 patients. All the patients had shown signs of dementia precox for over four years. In all but 1 patient evidence of schizophrenic deterioration was observed. These patients were selected because thorough physical and laboratory examinations showed no evidence of organic disease.

The method of induction of electronarcosis in human subjects was similar to the standard method described for dogs. For reasons of safety, the initial strength of current chosen was relatively low, between 150 and 250 milliamperes. This initial current was maintained for thirty seconds, after which it was decreased to the level at which respiration became possible. In man

17. Keller, C. J.: Experimentelle Katatonie durch elektrische Hirnreizung, Acta brev. Neerland. 1:100-101, 1931.

18. van Harreveld, A., and Kok, D. J.: Ueber experimentelle Katalepsie durch sinusoidalen Wechselstrom, Arch. néerl. de physiol. 19:265-289, 1934.

this level was somewhat higher than in dogs (45 to 90 milliamperes).

On initiation of the current the arms were suddenly brought forward and outward and the elbows were flexed. The legs were flexed at the hips and the knees. These contractions were lightning-like. They were sometimes absent when the experiment was started with a low initial current (150 milliamperes). The initial flexion was followed by a phase of rigidity. Sometimes a period of flaccidity was observed between the initial flexion and the rigidity. During the phase of rigidity the lower extremities were usually maximally extended. The abdominal and thoracic muscles were also maximally contracted, the chest being fixed in a position of maximal inspiration. The head was usually dorsally extended; however, absence of the dorsal extension or a rigid flexed position of the head was sometimes noted. The position of the arms showed the greatest variation. They were either abducted or adducted, flexed or extended. The hand was in the tetanic position or clenched into a fist, with the thumb often wedged in between the second and the third finger. Asymmetric positions of the arms, with extension on one side and flexion on the other, were frequently seen. Sometimes changes in posture from flexion to extension and vice versa were noted.

Application of the strong current was immediately followed by arrest of the heart, which lasted a few seconds; then the heart resumed its action at a low rate (not higher than 20 beats per minute). During application of the high initial current there was complete arrest of respiration. After the first few seconds the face, and sometimes the neck and thorax, became flushed. The eyes were kept tightly closed. When they were pried open, conjugate deviation was often observed. The pupils were usually constricted and did not react to light. A pilomotor response was frequently observed. In women an erection of the nipple was often seen.

The level of current at which adequate respiration became possible was rather constant in successive narcoses in the same patient, but was of course not known at the first application. Therefore, at the first induction of electronarcosis the current was decreased to a low level (50 or 60 milliamperes) after thirty seconds. If respiration started readily, a higher level of current was tried at the next application. If the return of respiration was delayed and the current had to be decreased in order to obtain adequate respiration, a lower level was tried the next time.

The decrease in the high initial current was followed by disappearance of the rigidity. Coarse shaking and clonic twitches occurred and receded spontaneously after five to fifteen seconds. Respiration began usually between fifty and seventy seconds after the first application of the current. At first a few gasps were made, which were shortly followed by more normal respiratory movements. Respiration was at first shallow but soon became deeper. It was often strained and noisy, probably because of contraction of the glottis. A decrease of only a few milliamperes abolished this effect. When the initial current was too low, respiration might be resumed almost immediately after its decrease. During the arrest of respiration the face, lips and nails became cyanotic. Usually the cyanosis was not severe and receded quickly when respiration was again established. When the contraction of the glottis prevented the free passage of air, however, cyanosis might be more severe. The changes in heart rate during this period were complicated and will be discussed later.

After respiration had been restored, a few minutes followed in which the body was relaxed and no active movements were seen. In this period no reflexes could be elicited. The knee jerk and the achilles and flight reflexes were all absent. The pupils were usually constricted and did not react to light, and the corneal reflex was absent. In this phase the face was often still flushed. If no further changes were made in the current, this passive state lasted three to five minutes. Then spontaneous movements which had the character of primitive movements appeared. From time to time righting attempts were made; the supine patient tried to roll over on his side or to sit up. These attempts were at first of short duration and were usually unsuccessful. Later intentional movements appeared. Crude attempts to remove the electrodes or to adjust the clothing and coverings were made. In some patients the motor activity became more pronounced and was finally difficult to control. Simultaneously with these phenomena reflexes returned. The knee jerk and the achilles reflex could be elicited with increased ease and might even be hyperactive. Sometimes the knee and foot clonus could be elicited. Stimulation of the sole usually produced the flight reflex, but in some patients this stimulus elicited the reflex of Babinski. Forced grasping could be elicited. Finally the corneal reflex returned, and the pupils, which in the meantime had been in middilatation, reacted to light. Defense movements sometimes occurred on painful stimulation, although these movements were crude and their localization was uncertain. The appearance of

intentional movements was indicative of the approaching restoration of cortical functions. All these symptoms were likely to occur earlier if the arrest of respiration was shorter than usual.

The respiratory frequency and the heart rate in human subjects during electronarcosis were higher than normal once the initial symptoms were over. The frequencies increased even more when restlessness was pronounced.

Consciousness was lost during the entire period of application of the current; some patients reported remembering a flash of light at the very start of the treatment, which may have been due to the stimulation of the optic system by the high initial current. No patient complained of any unpleasant sensations during electronarcosis. In some cases in which electronarcosis was continued until intentional movements were pronounced, the patient reported having a dim recollection of the very last part of electronarcosis. Even in these cases no pain or other unpleasant sensation was experienced. Termination of electronarcosis is indicated, nevertheless, when the appearance of intentional movements reveals the resumption of cortical activity. In other experiments the development of uncontrollable restlessness made termination necessary. For these reasons electronarcosis was limited in duration to five or ten minutes. Attempts were made to counteract the gradual awakening of central functions by increasing the current after the return of respiration. An early increase in current was found to be the most effective. After the appearance of primitive movements the effect of an increase in current was slight. After respiration was restored and cyanosis had receded, the current could be increased considerably, until stridulous respiration, indicating contraction of the glottis, forbade any further increase. For example, in an experiment in which the current had to be decreased to 70 milliamperes after the initial current (250 milliamperes) to obtain adequate respiration, it was possible to increase the current to 105 milliamperes during the following minutes before signs of respiratory impairment became noticeable. The current was changed slowly and cautiously, an increase of 5 milliamperes being made over a period of thirty seconds. Such an increase in current was accompanied by the development of moderate rigidity. The legs were kept extended, and the arms were flexed at the elbows.

This method of application of current usually delayed the development of the primitive movements slightly and retarded considerably the subsequent development of the other symptoms. In most patients it was possible to prolong electronarcosis in this way to from ten to twenty minutes, sometimes even to half an hour. In some patients, however, pronounced restlessness developed rather regularly after about seven minutes, so that it was necessary to terminate the narcosis at that time. It was never possible to prevent the awakening of central functions entirely.

Twice the slow increase in the current resulted in symptoms entirely comparable to the initial symptoms of electronarcosis. A strong extensor rigidity with arrest of respiration developed, a phase which, after the immediate cutting of the current, was followed by clonic twitches and restoration of respiration. These symptoms resulted from an increase in current at a late stage of electronarcosis, about ten minutes after the start.

Termination of electronarcosis resulted in general in a prompt and speedy return of con-
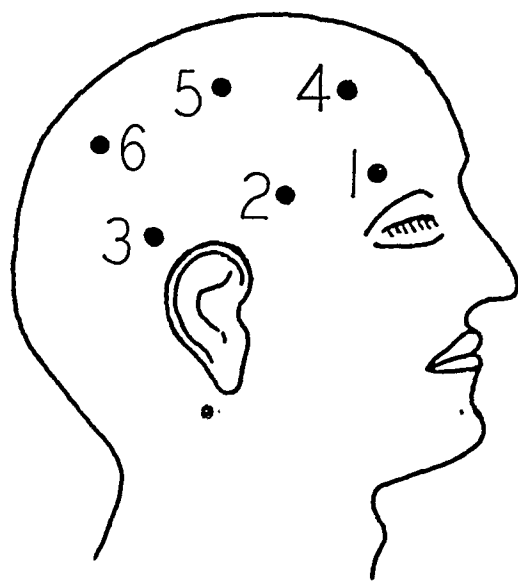
Fig. 1.—Location of the electrodes on the head in experiments to determine the influence of placement of electrodes on the symptoms of electronarcosis.

sciousness. After a few minutes the patient reacted to his name and a few minutes later tried to answer questions. Two patients, both of whom exhibited considerable restlessness during electronarcosis, showed a persistent tendency to confusion and restlessness after termination of the narcosis. The reflex of Babinski, which developed in several instances during electronarcosis, persisted for some·minutes afterward. Sometimes this reflex developed after the current was cut and changed a few minutes later into the flight reflex.

Effect of Placement of Electrodes.—In the dog placement of the electrodes in various positions on the head had no significant influence on the symptoms of electronarcosis. This was not unexpected, since in the dog the brain is small with respect to the size of the head, owing to the thickness of the bone and the muscle cover-

ings. These factors tend to produce a more or less equal distribution of the current in all parts of the brain irrespective of placement of the electrodes. In man the covering of the brain is much thinner in relation to its size, and localization of the current in certain parts of the human brain might therefore be possible.

The six electrode placements on the head shown in figure 1 were tried with 4 patients. The electrodes were placed symmetrically. Placement 2 was the standard location used in the applications of current previously described. The chief symptoms of electronarcosis were found to be the same regardless of the placement of the electrodes; thus they were similar to the symptoms described. The durations of the various phases were the same, and the characteristic variations for each patient were always present. Slight differences, characteristic of certain placements, were noted. These variations were readily explicable on the basis of stimulation of different

authors (Bikeles and Zbyszewski,[19] Ivy and Barry,[20] Roos and Koopmans,[21] van Harreveld and Kok [12]) have studied the effect on the blood pressure and the heart rate of the passage of a strong sinusoidal alternating current through the brain for a short period. As may be expected, the blood pressure curves obtained during the initial part of electronarcosis were in agreement with the observations of these authors. Immediately after the make of the high initial current, the heart stopped, with resulting drop in pressure (figs. 2 and 3 I). In most cases this arrest was of only a few seconds' duration, but occasionally it lasted longer. When the heart started beating again, the blood pressure increased with each beat and in this way climbed well above the prenarcotic value. The blood pressure reached a maximum either during the period of the high initial current or shortly afterward. The heart rate, which was always low during the initial current, often rose above the prenarcotic rate
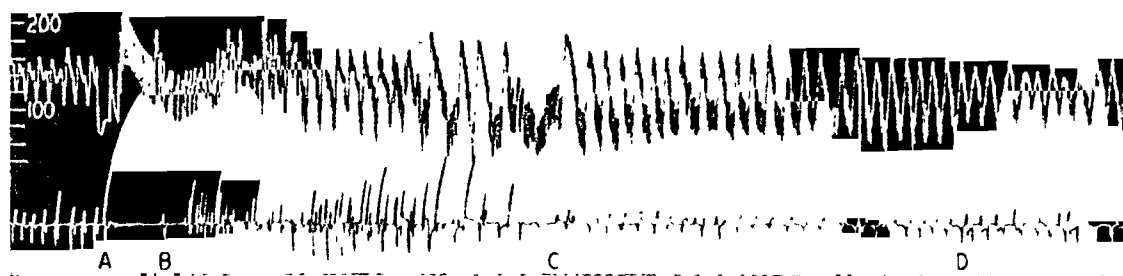
Fig. 2.—Blood pressure (upper curve) and respiration (lower curve) during electronarcosis. At the bottom is the time signal record (six second intervals). At A the initial current of 500 milliamperes was applied. After thirty seconds at B, this strength was decreased to 50 milliamperes, and at C it was further decreased to 45 milliamperes. The cardiac arrest in this experiment was rather long. The two parts of the curve are separated by an interval of five minutes, during which no significant changes in blood pressure and respiration were noted. The current was cut at D.

peripheral or central structures. Low placement of the electrodes (1, 2 or 3) resulted in profuse secretion of saliva and tears, which was scant or absent with placement of the electrodes high on the head (4, 5 or 6). When the electrodes were placed on the frontal part of the skull (1, 2 or 4) the pupils were constricted and did not react to light in the first part of the period of electronarcosis. With the electrodes on the occipital part of the head (3, 5 or 6) the pupils were more dilated and reacted earlier to light. With the occipital placements, 3 and 6, more impairment of the respiration was encountered than with the more frontal placements. For practical purposes a placement between 2 and 5, not too far occipital and as high as convenient with respect to the hair, seems to be the most suitable.

Influence of Electronarcosis on the Blood Pressure and the Heart Rate.—In the Dog: Several

shortly after the decrease of the current to the narcosis level (fig. 3 I).

It has been shown by the aforementioned authors that bilateral severance of the vagus nerves prevents the initial arrest of the heart. Under these circumstances the heart speeded up immediately after application of the current, and the blood pressure rose to a high level (fig. 3 III). It can therefore be concluded that the initial arrest of the heart and the drop in

19. Bikeles, G., and Zbyszewski, L.: Ueber den Einfluss der Reizung des Gehirnes (Oblongata) mittels Wechselströme auf das herzhemmende und vasomotorische Zentrum sowie auf die Atmung, Arch. f. d. ges. physiol. **182**:157-172, 1920.

20. Ivy, A. C., and Barry, F. S.: Studies on the Electrical Stunning of Dogs, Am. J. Physiol. **99**:298-307, 1932.

21. Roos, J., and Koopmans, S.: Studies on the So-Called Electrical Stunning of Animals, Vet. J. **90**:232-245, 1934.

blood pressure were due to stimulation of the vagus nerves, either directly or via their center. The rise in blood pressure, which became especially pronounced after transection of the vagus nerves, was probably due to stimulation of the sympathetic system, resulting in general vasoconstriction.
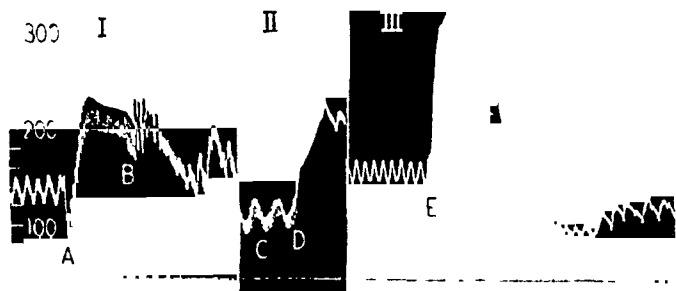
Fig. 3.—Influence of transection of the vagus nerves on the blood pressure during electronarcosis. The time interval is six seconds.

I, beginning of electronarcosis in an animal with the vagus nerves intact. At A the initial current of 500 milliamperes was applied, and after thirty seconds, at B it was decreased to 50 milliamperes. A short cardiac arrest caused a distinct drop in blood pressure.

II, part of the curve during electronarcosis, with a current of 50 milliamperes. The pulse rate was low. At C one vagus nerve was transected, and at D, the other. The pulse rate and blood pressure increased considerably.

III, after an interval of twenty minutes, during which no current was applied, the animal, in which the vagus nerves were now severed, was subjected again to electronarcosis. At E an initial current of 500 milliamperes was applied for thirty seconds, the strength of which was decreased to 50 milliamperes at F. The blood pressure and heart rate increased immediately after the beginning of application of the current.

The results of these experiments indicate that the typical blood pressure curve obtained in an animal with the vagus nerves intact results from simultaneous stimulations of the two systems. At first the influence of the vagus nerve prevails, with resulting cardiac inhibition and decrease in blood pressure. Afterward the heart escapes the influence of the vagus, and the effect of sympathetic stimulation becomes prevalent, with a rise in blood pressure above the prenarcotic level.

In the further course of electronarcosis the blood pressure, which was raised during the initial stages of electronarcosis, fell and from five to ten minutes after the start reached a value approximately equal to the prenarcotic level, where it remained for the rest of the experiment. In the narcotic type of electronarcosis, the heart rate was low (about half the normal rate) after the initial stages. It could be shown that this was due to a high vagal tone, since the injection of an appropriate amount of atropine or the transection of the vagus nerves speeded up

the heart considerably (fig. 3 II). Transection of the vagus nerves caused a sharp initial rise in blood pressure, followed by a decline in the next few minutes. The pressure usually did not drop to the level which existed before severance of the vagus nerves. During the hyperkinetic type of electronarcosis the heart rate was usually higher than normal. The blood pressure curves during electronarcosis were characterized by large variations associated with the phases of respiration. Often a pronounced respiratory arrhythmia was present, especially when the respiratory rate was low (fig. 2).

During 2 experiments in which violent hyperkinesis had been present for several minutes, the animals died suddenly, probably of heart failure, since respiration continued for a short period after the pulse had stopped. Autopsy on 1 of these animals revealed pronounced edema of the lungs.[22] It is probable that the heart failure was due to the unusual effort demanded of the heart during the period of hyperkinesis.

Cessation of the current was often followed by a drop in blood pressure. This decrease was seldom pronounced, but it became considerable when, during the experiment, the animal was made to lose a large amount of blood. Under
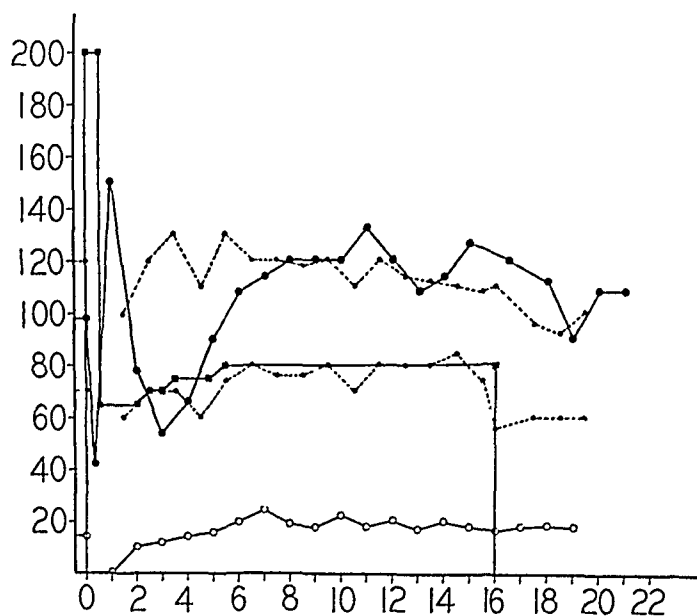
Fig. 4.—Blood pressure, heart rate and respiratory rate in a patient during electronarcosis of sixteen minutes' duration. The figures on the ordinate indicate the heart rate; the blood pressure, expressed in millimeters of mercury; the respiratory rate; and the current used to produce electronarcosis, expressed in milliamperes. On the abscissa is plotted the time, in minutes. The solid line marked with squares indicates the changes in strength of current; the solid line with the dots, the changes in heart rate; the broken lines, the systolic and diastolic blood pressures, and the solid line marked with circles, the changes in respiratory rate.

22. Dr. E. M. Hall, of the University of Southern California, examined the lungs.

these circumstances death occurred sometimes a few minutes after the termination of electronarcosis.

In Human Subjects: The changes in heart rate observed during electronarcosis in human subjects were similar to those noted in the dog. Application of the high initial current caused a cardiac arrest of a few seconds' duration, after which the heart started beating again, first at a low rate (fig. 4). Soon it speeded up until it reached, one to one and a half minutes after the beginning of electronarcosis, a maximum (150 to 180 beats per minute) which was considerably above the prenarcotic value. At this time the heart rate decreased again, often falling below the prenarcotic level. Three to four minutes after the beginning of electronarcosis, the heart speeded up once more until its rate reached a value of 120 to 160, which was maintained for the rest of the period of electronarcosis. Considerable variations in this general picture were observed.

Determinations of blood pressure could not be made during the period of rigidity and clonic twitches at the beginning of electronarcosis. However, since the heart was inhibited during the first few seconds of application of the current, it is likely that the blood pressure dropped immediately after application of the current, rising again with restoration of the heart action, as was the case in the dog. When, after one to one and a half minutes, it was possible to determine the blood pressure, the systolic pressure was usually near the prenarcotic level, though it often rose considerably in the following minutes. Values as high as 180 to 200 mm. were observed. The subsequent course was variable; the systolic pressure often slowly declined to, or stayed at, a level of 120 to 140 mm. (fig. 4). In some cases the systolic pressure fell even below the prenarcotic value. A rise in pressure in the further course of electronarcosis was observed on some occasions. The diastolic pressure usually followed the same trend as the systolic pressure, but the changes often were less pronounced. In some cases, during the latter part of electronarcosis a considerable drop in the diastolic pressure was observed which was not accompanied by a parallel decrease of the systolic pressure.

In 2 cases the initial inhibition of the heart lasted longer than the usual few seconds. Termination of the current after twenty and thirty seconds respectively resulted in immediate resumption of cardiac function. In a third case an arrest of the heart lasting about twenty seconds occurred about one and a half minutes after the beginning of electronarcosis. Here,

again, the heart action was restored as soon as the current was cut. No difficulties were encountered in these patients during subsequent applications of current.

Electrocardiograms were taken before and immediately after electronarcosis and two days later. The electrocardiograms taken immediately after electronarcosis showed slight flattening of the T wave in lead III. This had disappeared in all cases in the electrocardiograms taken two days after electronarcosis.

Chemical and Morphologic Changes in the Blood of Dogs.—Blood Sugar: It was found that the level of the blood sugar often more than doubled during electronarcosis (table 1). An increase in the blood sugar has also been reported after electric shock treatment (Kalinowsky and others [23]). Since both during electric shock and during the initial stages of electronarcosis a cer-

TABLE 1.—*Changes in Blood Sugar Associated with Electronarcosis*

Dog No.	Date	Blood Sugar Before Electronarcosis, Mg./100 Cc.	Time Second Sample Was Taken, Min.	Blood Sugar During Electronarcosis, Mg./100 Cc.
1	9/24	76	13	223
2	10/ 1	97	12	198
3	10/ 1	79	11	171
4a	9/24	89	11	195
4b	9/30	85	18	236
5	9/24	92	12	221
6	9/24	98	12	264
7a	10/ 6	106	10	225
7b	11/ 3	120	12	202
7c	11/ 7	87	12	204
7d	11/10	94	10	224
8	9/24	81	13	125

tain amount of asphyxia is present, the possibility has been considered that this asphyxia is responsible for the increase of the blood sugar. This possibility was investigated in a series of experiments on a tracheotomized dog in which artificial respiration was applied from the beginning of electronarcosis.[24] Nonetheless, the same rise in the level of the blood sugar was observed even when the initial cardiac arrest, which might cause a short interruption of the oxygenation of the brain, had been prevented by administration of a suitable amount of atropine. It is therefore likely that the increase in the blood sugar is a manifestation of stimulation of the sympathetic system, which also causes the rise in blood pressure during the early stages of electronarcosis.

Blood Count: The number of red and white corpuscles increased materially during electro-

23. Kalinowsky, L. B.; Barrera, S. E., and Horwitz, W. A.: The "Petit Mal" Response in Electric Shock Therapy, Am. J. Psychiat. 98:708, 1942.

24. With an intact animal such a study is impossible because of spasm of the glottis.

narcosis (table 2). Such an increase in the blood count may be produced in two ways: Either corpuscles are added to the blood, or water is removed from the plasma. It is unlikely that the latter mechanism is exclusively responsible since the red and white corpuscles usually do not increase in the same proportion. To investigate the possibility of dehydration of the plasma, the dry weights of the serum before and during electronarcosis were determined. A slight increase of the dry weight (0.4 to 6.5 per cent) was found. However, this change was insufficient to explain the large increase in the number of red and white corpuscles noted in most experiments. There must be still another mechanism active during electronarcosis. The strong sympathetic excitation at the beginning of electronarcosis may cause the contraction of blood reservoirs, such as the

COMMENT

Electronarcosis in man, induced in the way described here, differs in some respects from electronarcosis produced in dogs. Whereas in the latter the symptoms of electronarcosis may range from a quiet narcotic to a violently hyperkinetic form, electronarcosis in man is never of the absolutely quiet or the violently hyperkinetic type. There are always hyperkinetic symptoms, which, however, never reach high intensity. As time goes on, electronarcosis in man becomes lighter; the patient becomes increasingly restive, and the appearance of intentional movements indicates the return of function of the cerebral cortex. The appearance of these symptoms can be postponed by a suitable increase in the narcosis-producing current, but they cannot be prevented. In the dog the narcotic form of electro-

TABLE 2.—*Changes in the Blood Count Associated with Electronarcosis*

Dog No.	Date	Red and White Blood Cell Count Before Narcosis	Time Second Sample Was Taken, Min.	Red and White Blood Cell Count During Narcosis	Percentage Change	Dry Weight of Plasma Before Electronarcosis, %	Dry Weight of Plasma During Narcosis, %	Percentage Change in Dry Weight
1	10/12	6,290,000 17,200	13	7,120,000 19,050	13 11	....	....	...
2	10/13	6,630,000 11,700	10	6,850,000 17,050	3 46	8.29	8.32	0.4
3a	10/12	7,160,000 24,500	20	8,205,000 28,000	15 14	....	....	...
3b	10/18	6,490,000 11,550	15	8,180,000 17,150	26 48	7.86	8.37	6.5
4	10/16	8,970,000 24,600	20	9,260,000 30,750	3 25	8.34	8.78	5.3

spleen, so that corpuscles are added to the circulating blood.

Carbon Dioxide–Combining Power: Finally, the carbon dioxide–combining power of blood was determined before and during electronarcosis (table 3). During electronarcosis a definite decrease in this value was found, which may

TABLE 3.—*Change in Carbon Dioxide-Combining Power Associated with Electronarcosis*

Dog No.	Date	Before Narcosis, Vol. %	Time Second Sample Was Taken, Min.	During Narcosis, Vol. %
1	12/ 1	50.3	12	29.1
2	12/ 3	52.9	13	32.0
3	11/21	57.7	15	53.3
4	11/18	44.8	15	33.8

have been due to a release of lactic acid from the muscles during the strong initial contractions.

All chemical and morphologic changes in the blood were found to be reversible in a few hours.

narcosis can be prolonged indefinitely by a moderate increase in the current.

These differences in electronarcosis as induced in man and in dogs may be due to differences in structure and functional properties of the brain of the two species; it is equally possible, however, that differences in the experimental methods are responsible. From the animal experiments it is known that both factors are of importance. In some dogs the hyperkinetic type of electronarcosis will occur regardless of the method of application of current. On the other hand, some methods of applying the current favor the narcotic and others the hyperkinetic type of electronarcosis. For instance, a low initial current is likely to bring out more hyperkinetic symptoms, whereas a high initial current tends to shift the symptoms toward the narcotic form.

In the present observations on patients the initial current has always been low, and this may have prevented the development of a strictly narcotic form of electronarcosis in man. Only further experiments with higher initial currents

can decide whether the structure of the human brain or the method of application of current is responsible for the failure to produce the narcotic form of electronarcosis in man. On the other hand, the absence of violently hyperkinetic symptoms may well be caused by our practice of terminating electronarcosis when the patient becomes too restive, so that the hyperkinetic symptoms are not given time to develop fully.

The initial symptoms of electronarcosis resemble those of electric shock. Slight differences can be found, however. The hypotonic period between the initial flexion and the development of extensor rigidity is relatively long (up to twenty to thirty seconds) in electric shock but is quite short, or even absent, in electronarcosis in human subjects. Whereas in electric shock extensor rigidity is self limited, in electronarcosis this symptom lasts until the decrease of the initial current. Self-limited clonic twitches are observed in both conditions. In both states respiration starts after about the same interval provided that the current has been sufficiently decreased to make return of respiration possible. The differences between the symptoms of electric shock and those observed in the beginning of electronarcosis are most probably due to the differences in application of the current; in production of electric shock a strong current passes for a fraction of a second only, whereas in induction of electronarcosis a weaker current is applied for thirty seconds.

Electric shock therapy, when carefully applied, is a safe procedure. Since, as judged from the symptoms, the initial stages of electronarcosis can be considered as a modified electric shock, it is likely that the beginning of electronarcosis is equally safe. Indeed, in the great majority of electronarcoses respiration was established within a reasonably safe period, and in most cases in which the level of electronarcosis was too high a slight decrease in the current immediately restored adequate respiration. On the few occasions in which respiration did not respond sufficiently on decrease of current, it was quickly restored by turning off the current. The cardiac arrest immediately after application of current was usually not more than a few seconds. Whenever the heart action was suspended for more than the usual period, the beat was restored promptly by turning off the current. After the initial period respiration could be easily controlled. Insufficient oxygenation of the body, as indicated by strained respiration and developing cyanosis, could be corrected by a slight decrease of the current. Undue changes in the circulatory apparatus during the later part of electronarcosis, such as the development of a high blood pressure or a rapid heart rate, have been found to be, immediately reversible by turning off the current. All patients with obvious disease of the heart and vessels were excluded. Besides, the circulatory apparatus was carefully watched during the series of applications of current. Electrocardiographic examinations were made at regular intervals. In none of the patients were any undue effects on the circulatory apparatus observed.

None of the patients had fractures or dislocations of the spinal column. This is probably because clonic twitches, and perhaps extensor rigidity, during electronarcosis are less pronounced than during electric shock.

It can be concluded that induction of electronarcosis, like that of electric shock, when carefully carried out, is reasonably safe. Indeed, more than 100 electronarcoses have been induced in human subjects without any serious involvement. Since all methods for induction of shock thus far employed in the treatment of mental disorders are purely empiric, it is premature to speculate on the therapeutic value of electronarcosis. Although no claim for the curative properties of electronarcosis is made at present, the method offers for trial a clinically feasible procedure.

SUMMARY

1. In man, as in animals, a state of unconsciousness (electronarcosis) can be maintained by the passage of a current through the head. In man electronarcosis has been prolonged up to thirty minutes.

2. Two forms of electronarcosis have been observed in the dog—a narcotic form, which resembles chemical narcosis, and a hyperkinetic form, which is characterized by strong motor activity.

3. In man the symptoms of electronarcosis were a mixture of symptoms of the narcotic and the hyperkinetic type of electronarcosis.

4. All symptoms studied, occurring during and after electronarcosis, were found to be completely reversible.

DISINTEGRATION AND RESTORATION OF OPTIC RECOGNITION IN VISUAL AGNOSIA

ANALYSIS OF A CASE

ALEXANDRA ADLER, M.D.

BOSTON

The complexity of the process of optic recognition is such that no two patients suffering from the disorder called visual agnosia have identical derangements in function. An analysis of the symptoms and their changes in the course of recovery in a young and cooperative patient appeared worthy of record for the further light such a study may shed on the process of visual perception.

REPORT OF CASE

H. C., aged 22, married, had been a guest at the Cocoanut Grove night club, Boston, on Nov. 28, 1942, the night it was destroyed by fire, with 491 patrons killed and many more injured. She was one of the 132 patients admitted to the Boston City Hospital during this night. On entry she had only small, superficial burns over the right scapula. It was immediately noticed that "she could not see." She was hoarse for almost two weeks, during which tracheal inflammation led to moderate difficulties in breathing, and for five days she had minimal rales in her lungs. From December 2 to December 9 sulfadiazine was given, the total dose being 42 grains (2.73 Gm.). She coughed and expectorated thin, white sputum during the first five days. She talked almost incessantly during the first two weeks. Her talk was incoherent, but with clear enunciation of words. There was marked reiteration. She kept repeating during the first two days, "May I move my arm? May I move my leg? May I move my head?" When she was told that she could move, she said, "Oh, good," and then did so. Several times she complained that she could not see. She had to be fed, since she could not find her food, but she identified it by its taste. After two days she recognized nurses as such "by their white uniforms," as she explained at that time. For long periods she gazed stonily ahead as if she did not see anything, but she listened attentively to voices in her vicinity and showed pronounced echolalia in response to questions during the first week. For instance, when she was asked, "Helen, what do I hold in my hand?" she would reply, "What is in my hand; what is in my hand; what is in my hand, Helen; what is in my hand?" She was unable to name objects shown to her, and her gaze did not fix on them during the first week. However, she quickly identified people by their voices and objects, like keys, by their sound. Neurologic examination revealed an equivocal plantar response on the right; this became normal during subsequent testing. She was disoriented for time and was unable to give the date of her marriage. She knew her own and her husband's name but at first could not give her address. She was unable to do simple calculations and could not read. She could write, however, although at first with perseveration and

errors. During the first days she did not know that she had been in a fire, but after this had been impressed on her several times, she kept repeating all through the first week, without any adequate emotion, that there had been a fire at the Cocoanut Grove, that many people had been killed and that she did not know how she got out. Her husband, who had been with her on that evening, stated that he had seen a sheet of flame coming toward him. He grabbed his wife and started toward an exit. When they reached the door the flames overtook them. He lost consciousness and woke up in the hospital. He was hoarse for one week but, except for superficial burns over his face, presented no other signs.

The patient had completed high school and business school and had worked as a comptometer operator for a large firm for one year, until her marriage in August 1942. Her parents were of Italian origin. The family's and the patient's histories previous to the injury were without significance.

Three months after her injury the patient gave the following account of the first days of her illness: "The last thing that I remember of that night at the Cocoanut Grove is that suddenly everything became black. My husband started pulling me out. The next thing I remember is the Boston City Hospital, but I do not remember anything about the first few days. At first everything seemed dark to me. Then I could see white—nurses and doctors. I recognized them by their uniforms, and I could distinguish the doctors because of the odor of tobacco. Soon I could distinguish doctors from nurses by the way their hair was done. Doctors do not have curls. The voices helped a lot. I talked so much because I felt like two people in one, saying something different from what I wanted to say. I know that I repeated a lot because I felt that I had not said it correctly. I could not breathe during the first days. At first I thought I was at home because my sister was with me. When I saw nurses I knew I was in a hospital."

I saw the patient for the first time five days after her injury and from then on daily during her stay in the hospital. The patient was at first totally blind and then, after two days, could distinguish white from dark but could not recognize colors. In the beginning she could not recognize letters or words but could write, thus exhibiting the picture of a pure (subcortical) visual alexia, Wernicke's type. She had visual agnosia for objects, pictures and persons. There was complete acalculia. During the first two weeks she presented a picture of psychomotor excitement, flight of ideas, reiteration in her activities and in her flow of talk, echolalia and perseveration in her writing. Hearing, smell, taste, touch, articulation and understanding of words and motor ability were not impaired. A diagnosis of lesion of the brain, probably caused by carbon monoxide fumes, was made.

She was discharged from the hospital on Dec. 23, 1942, and since then has been seen at weekly intervals.

COLOR AGNOSIA

As has already been mentioned, the patient recognized white after the second day of her illness. After two weeks she recognized all colors. In the interval she frequently made mistakes in trying to identify red and green but never erred in the recognition of blue and yellow
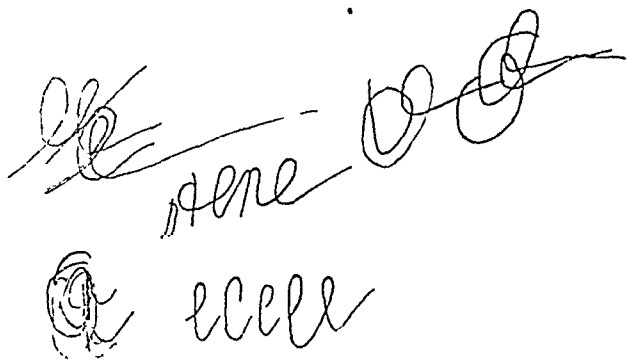
Fig. 1.—The patient was asked to write an *c*, "Helen" and an *o* (December 4). Below, she was asked to write an *a* and an *c* (December 8).

once it had come back to her. However, up to the time of this report, seven months after the injury, she frequently called a dark blue "purple." After the first two weeks she was able to name correctly the color which corresponded to various objects or the objects which corresponded to colors and could match various shades of the same color. She was also able to match colors according to their intensity.

There is general agreement that the lesions of the brain associated with color agnosia are in the ventral parts of area 18 (Nielsen and Fitz-Gibbon,[1] Poetzl[2]). It is assumed that the lesion is bilateral when function does not return and that it is unilateral when function does return.

WRITING

From the beginning the patient was able to write, but she did so with perseveration and errors (fig. 1). This condition prevailed during the first two weeks, after which her writing improved. Four weeks after her admission her writing was similar to that before her illness except for some difficulty in her keeping to the line and occasional skipping of words. Figure 2 allows comparison of her writing shortly after her admission with a sample obtained later. She could not copy, however, a feature typical of the optic type of alexia.

Her spatial disorientation expressed itself in the way in which she dealt with single cardboard letters when asked to put them together to form

a word. For instance, five months after the injury, she formed the word "Tracy" in the following way: "Ɩ r ℧ ɔ y" When attention was called to her mistakes, she corrected them with difficulty. By the end of the sixth month she no longer made the mistake of inverting the cardboard letters, and she remarked that she was taking particular care to set the letters in the right direction.

An interesting phenomenon could be observed, however, after several months had elapsed. She had to think for some time before she could write certain letters and started to confuse some of them. For example, six months after the injury, when ·asked to write a small *t*, she wrote a small *i*. This was the way in which she often perceived the small *t* when reading. Evidently her impaired visual perception finally changed her writing. In addition, she forgot how to write some of the less common letters, such as small *q*, and noticed herself that she forgot or confused letters when she had not used them for some time.

The patient had been an expert touch typist before her illness, and when she was asked to type, a few months after her admission, she proved herself able to do so rapidly, although she made occasional mistakes. Her mistakes consisted of confusing letters which were similar in appearance, such as small *t* and small *l*. Thus, her impaired perception and imagery interfered in the same way with her typing as it did with her writing.
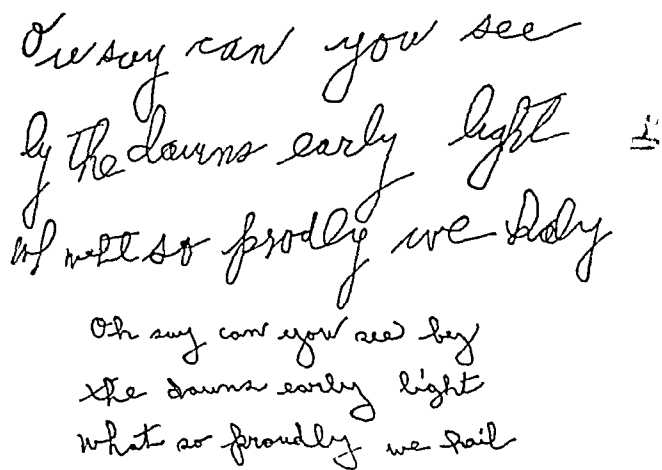
Fig. 2.—The patient was asked to write a verse of the national anthem. The upper sample was written on Dec. 17, 1942; the lower sample, on May 4, 1943.

PURE VISUAL ALEXIA

Impairment in Reading of Mathematical Figures.—During the second week of her illness the patient started to use her index finger to trace the contour of objects. This kind of procedure has been observed in agnostic patients

1. Nielsen, J. M., and FitzGibbon, J. P.: Agnosia, Apraxia, Aphasia, Los Angeles, Los Angeles Neurological Society, 1936.

2. Poetzl, O.: Die optisch-agnostischen Störungen, Leipzig, F. Deuticke, 1928.

by Westphal,[3] Goldstein and Gelb,[4] Nielsen and FitzGibbon[1] and others. With the normal person, too, the visual impression is made more vivid if he traces the object with the finger. He is less likely to overlook details. Furthermore, tracing aids perception by successive addition of parts instead of recognition by simultaneous perception of the parts of the whole. As will be shown later, recognition by addition has become the patient's way of dealing with optic problems.

Whereas the patient was not able to recognize any letter during the first two weeks, she occasionally succeeded in recognizing mathematical figures. While she did not recognize the figures 2, 3, 5, 6, 8 and 9, naming them interchangeably 6 or 5, she recognized the 1, 4 and 7 during the second week of her illness. The recognition first of figures with straight lines and later of those with curves is of special interest. Closer examination of this phenomenon revealed a fundamental disturbance of visual recognition: The patient perceived only parts and guessed the rest. Since it is possible to guess where a straight line is going but not the direction of a curve, she was able to recognize the figures 1, 4 and 7 first. The first number with a curve that she recognized was 5. This she recognized by the combination of the upper two straight lines. At present, seven months after injury, she correctly recognizes any single number. She is conscious of the fact that she distinguishes the single numbers by their special characteristics. A few months ago she explained: "In a 6 there is only a lower loop. If I find an upper loop, too, I know it is a 3. If there is only an upper loop, it is a 9. There are two circles in the 8." But since she recognizes objects by tracing the contours, by adding the parts and by making conclusions from all she has perceived, she has to take more time than does the normal person, who recognizes all the parts, in the main, simultaneously. Her disturbance can be analyzed more closely by tachistoscopic procedures. The following protocol was taken two months after her admission: An 18 was shown to her. She recognized the 1 correctly on exposure for one hundred-fiftieth of a second, but she recognized the 8 only on exposure for one-fiftieth second. The following protocol reveals how she finally recognized the 8:

1/150 second.... "A 6?" She then corrected, saying, "A 3. I first thought the loops were in different directions. Or is it a 5?" When asked to draw what she had seen, she wrote 3, a 5 without the vertical line.

1/100 second.... "A 6."
1/50 second.... "Oh, it is an 8. All the time I have seen only the lower loop, and therefore I thought it was a 6."

It has been pointed out that numbers were the only symbols that could be recognized by some agnostic patients or that numbers were the first symbols they recognized during recovery. The way in which this patient went about it explains why it is easier for agnostic patients to recognize numbers than letters. There are only ten numbers, and it is comparatively easy to distinguish them by a few characteristics. If the patient did not know whether a number or a letter was shown her, recognition was more difficult, or even impossible. Therefore she always asked first, "Is this a number or a letter?" She herself, remarked during the second month: "I have to think to find out what it is." Head[5] cited a patient who made a similar remark: "I have to reason out the meaning of the whole picture."

Impairment in Reading of Letters and Words. —The patient is still unable to read what she herself has written. When she is asked to point out a certain word in a sentence which she has just finished writing, she counts out the words one by one to get to the word requested. During the first two weeks of her illness she could not recognize any letter, whereas at present she recognizes all printed capitals when presented singly and most of the printed letters from the small alphabet. Of the written alphabet she recognized on last examination, six months after injury, only about half the capitals and half the small letters. As it was with figures, she recognized letters with straight lines first, the first letter to be recognized being the *H*. This she recognized with joy nineteen days after her injury and said, "Because my name is Helen." On the same day she called *K* a "capital *I*." Here she perceived the first straight line only and, on request that she draw what she had seen, made the one straight line of the *I*. The following day, December 17, she confused *P, B* and *R* as such, and she still does so occasionally. She remarked in March 1943, "Capital *P, B,* and *R* look alike to me." Her confusion is derived from her procedure of tracing first the left upper part, which is alike in these three letters. Another difficulty which still persists is her confusing of *F* with *E*, which, again, is explained by the similarity of the upper left part in the two letters. She experiences the greatest difficulties with written letters, all of which exhibit curves. All the letters of the written alphabet were exposed singly, not alphabetically, first the capitals and

3. Westphal, A.: Aphasie, Ztschr. f. Ethnol. **6:**94-102, 1874.

4. Goldstein, K., and Gelb, A.: Psychologische Analyse hirnpathologischer Fälle, Leipzig, J. A. Barth, 1920, vol. 1, pp. 1-143.

5. Head, H.: Aphasia and Kindred Disorders of Speech, Brain **43:**87-165, 1920.

then the small letters, and the patient was asked to read aloud and then to copy the letters as she had seen them. Her errors were as follows: 1. She perceived only parts (fig. 3 *A*). 2. She added to the parts which she had perceived by guessing at the completion (fig. 3 *B*). 3. In some instances she left out *and* added, as in *i* and *j* (fig. 3 *C*). 4. Occasionally she showed a tendency toward mirror writing (fig. 3 *D*). 5. Whenever the patient recognized a letter, she "copied" it in her own handwriting (fig. 3 *E*). These errors are fundamentally the same as those initially encountered when she was dealing with numbers.

Five months after her injury, small pieces of cardboard, each containing a single letter, were
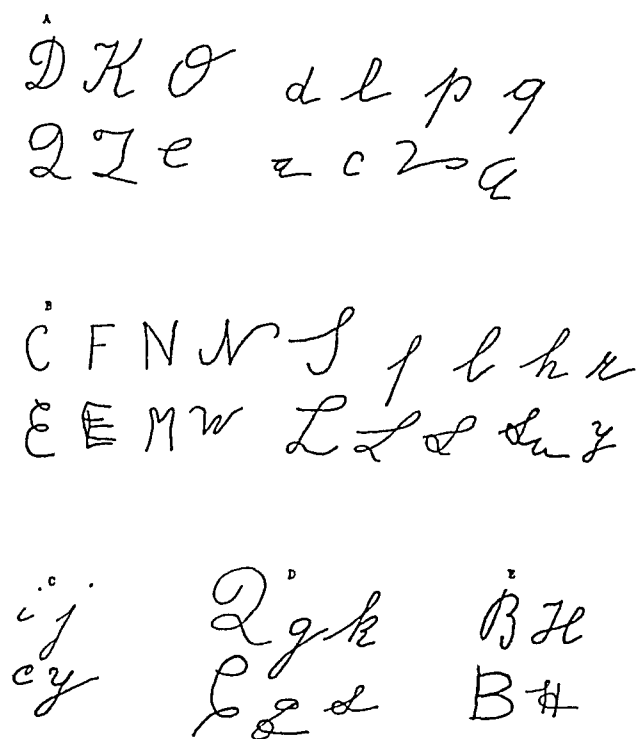
Fig. 3.—The patient was asked to read samples (upper line) and then to copy the letters (lower line) as she saw them. She left out parts (*A*), added parts (*B*), left out and added parts (*C*), showed mirror writing (*D*) and "copied" recognized letters in her own handwriting (*E*). Date: March 2, 1943.

shown to her. She recognized the *e*, "because it has a space on this side," as she said, pointing to the right. Then the same *e* was presented to her upside down. "That is a small a because the space is on the other side," she said, pointing to the left. To the normal person an *e* presented upside down still does not suggest an a, regardless of the open space on the left, but since the patient had by then learned to recognize letters by their outstanding characteristics, her error is understandable. During the same experiment she immediately recognized the *t* as such. When it was presented upside down, she named it with

conviction "small *f*." She explained that she had recognized it by the hook on top and the horizontal line. Her spatial disorientation prevented her from noticing that the hook went to the opposite side and that the horizontal line was lower than it is in an *f*.

The first word that she recognized was her name "Helen" which she did the day she recognized *H*. At that time she could not recognize any of the remaining letters of her name when they were presented singly. This shows that she had guessed her name after recognizing the *H*. This process of guessing the whole word from a few letters, aided by an estimation of the length of the word, is a procedure which she has followed ever since. This, however, results in her succeeding with printed words only, since she can hardly make out enough written letters to guess a written word. In several instances it has been reported as surprising that certain patients could read some long words correctly but persistently erred with short words. Short words can easily be changed by reversal of only one or two letters, which is impossible in long words. This explains the phenomenon which this patient presents, too. For instance, she read "GIRL" as "GOING" (fourth week after injury), having first recognized the *G* and the *I*. In the second month after injury, when shown the word "PRESIDENT" and asked to copy it as she saw it, she wrote "PRESDEWT," skipping the *I* and adding V to the N. But after a few seconds she remarked that this word probably meant "president."

The patient frequently reads a word from the line above as belonging to the lower line, regardless of whether or not she has previously recognized the word. She is never confused by a word from the line below. This tendency to fix her optic attention at some place and revert to it subsequently was present from the beginning of her illness. This is shown in the following protocol, taken three weeks after injury, when the symbols were presented to her successively, one below the other:

"What is this?" [9] .... "Capital A"
"What is this?" [8] .... "9"
"What is this?" [B] .... "8"
"What is this?" [W] .... "Capital B"

This protocol looks almost as if the patient were a malingerer who named previously shown samples instead of those presented to her at the time of identification. But when the patient, after having named the previously presented symbol, was asked to show where she had seen this, she pointed, after some hesitation, to the correct line, above. Analogous observations were made by

von Stauffenberg[6] and by Heidenhain,[7] who reported that their agnostic patients gave the name of an object which they had not recognized as their response to a different object during subsequent examination. Such perseveration may at times give the impression of preoccupation with background, as in copying of block designs and in other optic performances, when, in fact, the error results from the "background" being first seen with subsequent perseveration of the impression. Preceding optic impressions interfere with the subsequent ones, a "disturbance of figure-ground relationship" (Goldstein and Gelb[4]) being thus simulated. This adherence to a previous optic impression seems to be analogous to perseveration of speech or writing in patients with lesions of the brain. Similarly, it was possible to trace the interference of antecedent visual impressions on other optic performances, such as her drawing and reading.

In several cases of optic agnosia, in which the reading disability was carefully examined, reactions analogous to those of this patient (Goldstein and Gelb,[4] Scheller and Seidemann[8]) were reported. There are cases on record of a patient's inability to relax visual fixation (Bálint,[9] Holmes[10]) without evidence of agnosia. Therefore it appears that inability to comprehend the whole in cases of agnosia is more important than, and is independent of, the patient's perseveration of optic fixation on some detail.

A sample of the patient's reading of a text[11] printed in medium-sized letters follows. The original text is given above and the patient's reading below, in quotes. The sample was obtained six months after injury.

The contents of this book center around activities of children.
"The alphabet to—of this book center around activities of children."
both at work and at
"both of work and at"
play.
[The patient skipped over this line—a frequent happening.]
It includes animals and toys as well.
"If children act and ways would."

The patient, therefore, is subject to the following errors: 1. In contrast to the way in which normal people read, she does not recognize the word as a whole but adds up letters which she has recognized. The rest of the word may be guessed correctly or incorrectly. If she is unable to guess a word, she is frequently not able to make it out, even if she has finally recognized all the letters, because of the spelling of the English language, which is not phonetic. 2. She skips over words. 3. She leaves out lines.

She herself remarked that since her illness letters looked different to her. "They look as if they were all together, as if it were just one line. I have to separate them myself." The smallest print was most difficult for her to read because she easily slipped into surrounding letters. Larger interspaces prevented this. Therefore even if the patient had been unable to make out any letter in a word, she was occasionally able to recognize each of them if they were uncovered one by one.

The patient was able to identify by touch, without difficulty, letters cut out of cardboard. It was therefore only a disturbance of optic recognition which interfered with her reading.

The patient had never been able to read music. Therefore no change in this ability could be found in her. It may be assumed that she would not be able to read music at all, since she would not be able to perceive its spatial arrangement correctly. Such a disturbance has been described in a few suitable agnostic patients (Henschen,[12] Poetzl[2]). On the other hand, she quickly identified any popular tune by ear, even during the first week of her illness.

Impairment in Copying of Letters and Words.—Her reading difficulties are graphically registered by the way in which she copies letters or words. Her errors in copying single letters have been shown in figure 3. The difficulty increases notably when she copies two or more written letters or a word (fig. 4 *A*). The figure shows how little, if any, improvement there is in her ability to copy handwriting.

GEOMETRIC OPTIC AGNOSIA

Impairment in Copying of Geometric Figures and Patterns.—During the first month of her disease the patient was unable to recognize simple geometric figures. For instance, a protocol from the fourth week contains the following sample:
"What is this?" [a circle] "Looks like an alphabetical *A*."
"What is this?" [a triangle] "Looks like a great, big *A*."
"What is this?" [a square] "Looks like a capital *B*."

Five weeks after injury she again called an equilateral triangle "a big *A*." When she was

6. von Stauffenberg, W.: Ueber Seelenblindheit, Arb. a. d. hirnanat. Inst. in Zürich **8**:1-212, 1914.

7. Heidenhain, A.: Beitrag zur Kenntnis der Seelenblindheit, Monatschr. f. Psychiat. u. Neurol. **66**:61-116, 1927.

8. Scheller, H., and Seidemann, H.: Zur Frage der optisch-räumlichen Agnosie, Monatschr. f. Psychiat. u. Neurol. **81**:97-189, 1931.

9. Bálint, R.: Seelenlähmung des "Schauens," Monatschr. f. Psychiat. u. Neurol. **25**:51-81, 1909.

10. Holmes, G.: Cerebral Integration of Ocular Movements, Brit. M. J. **2**:107-112, 1938.

11. Mabie, P.: First Steps to Reading, Poughkeepsie, N. Y., Artists and Writers Guild, Inc., 1939.

12. Henschen, S. E.: Klinische und anatomische Beiträge zur Pathologie des Gehirns, Stockholm, Almquist & Wiksell, 1922, vols. 5-8.

told that it was not a letter, she recognized the triangle. She had seen the outline of the triangle and, in anticipation of a letter, had made the wrong conclusion. Evidently the compensating mechanism for her difficulty in optic recognition was guessing. Up to the present she has not gone far beyond recognition of the simplest geometric forms. After six weeks she correctly copied a triangle, a square and a circle, but up to the present she cannot copy a hexagon (fig. 4 *B*). The situation becomes even more con-

gradually increased time of exposure, and the patient was asked to draw what she had seen. The protocol shows the patient's inability to perceive details simultaneously, as is normally done when one sees simple figures. The patient perceived only parts and, by gradually tracing around the contour, added up the parts. In all such instances she started with the upper part of the figure, and usually with the left corner. Evidently this sequence followed the pattern of the writing movement. At the end of the
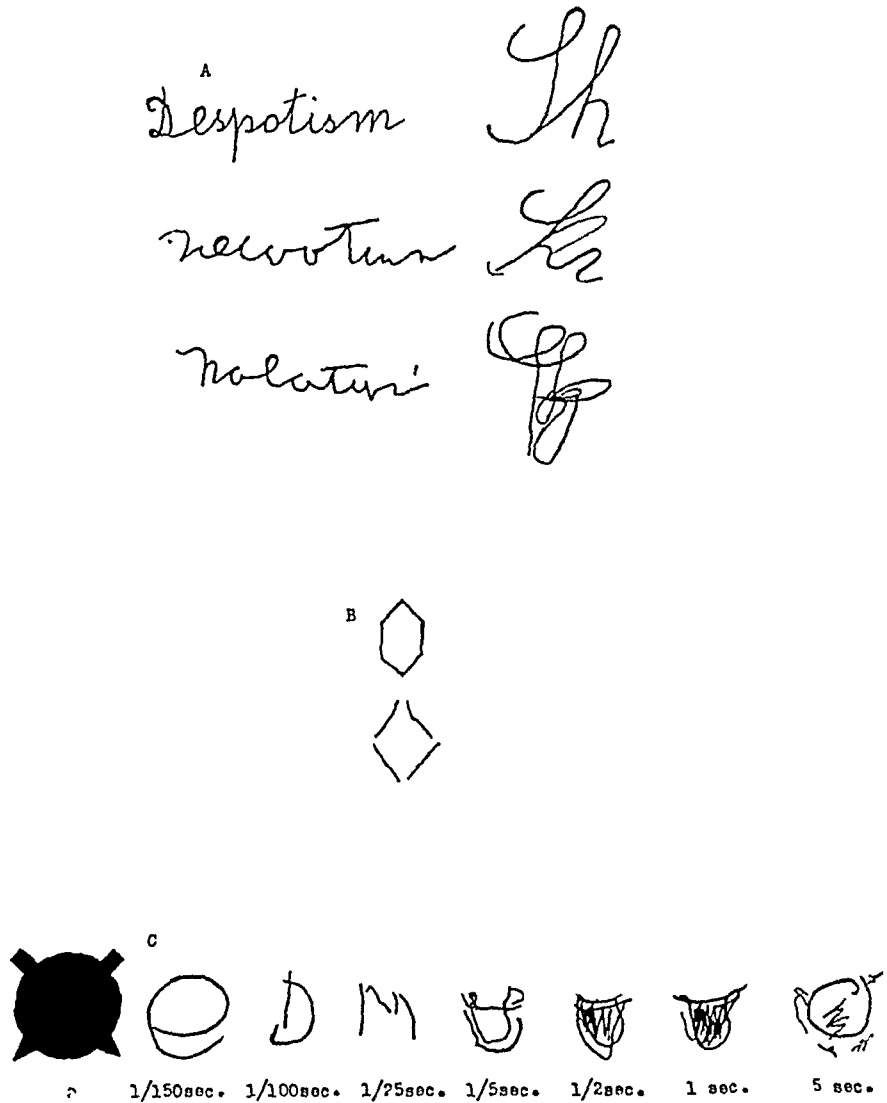
Fig. 4.—(*A*) Attempts to copy the same sample (uppper line) at different times, the middle line on May 27, 1943 and the lower line on Feb. 1, 1943. Hardly any improvement is apparent.

(*B*) Attempt to copy a hexagon (at the top). As usual, the patient first copies the upper and then the lower parts. Date: May 4, 1943.

(*C*) On tachistoscopic exposure of *a*, which normally is correctly recognized at one hundred-fiftieth second, the patient drew first the upper two marks (one twenty-fifth second), then perceived the lower contour (one-fifth second), then filled in the contour (one-half second). Finally, at five seconds she perceived all the details. Date: March 2, 1943.

fusing when she tries to copy figures with curved lines. The tachistoscope gives additional information about the difference between the normal person's and the patient's way of optic recognition (fig. 4 *C*). Figure 4 *C,a* which normally is correctly perceived at one hundred-fiftieth second, was shown to the patient at a

experiment (fig. 4 *C*), when, at an exposure time of five seconds, she had recognized all details, the patient said, "I could not get all the little marks first because it was so fast. I only got the two upper ones first."

With unlimited time of exposure too, the patient was unable to perceive the whole (fig.

5 *A*). She perceived the figure as being divided into parts, except for figure 5 *E*, which she copied approximately correctly, saying, "That reminds me of the United States, a capital *U*." When no straight line was drawn through the
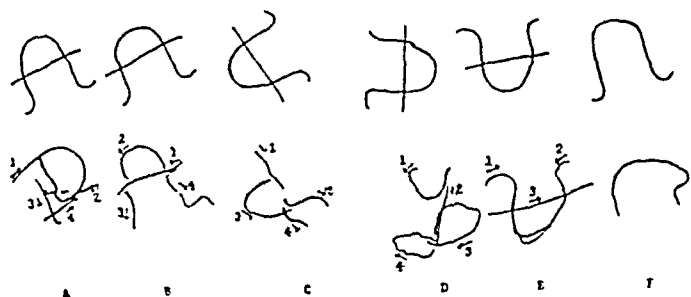
Fig. 5.—In the lower line, the patient tried to copy (*A* and *F*) and to trace through transparent paper (*B*, *C*. *D* and *E*) the figures at the top. As usual, she started at the upper left corner, or occasionally picked out the straight line first (*B*). Date: May 4, 1943.

curve, the patient was able to copy, as well as to trace, the curve correctly (fig. 5 *F*). Figure 6 *A* demonstrates how confusing the task became
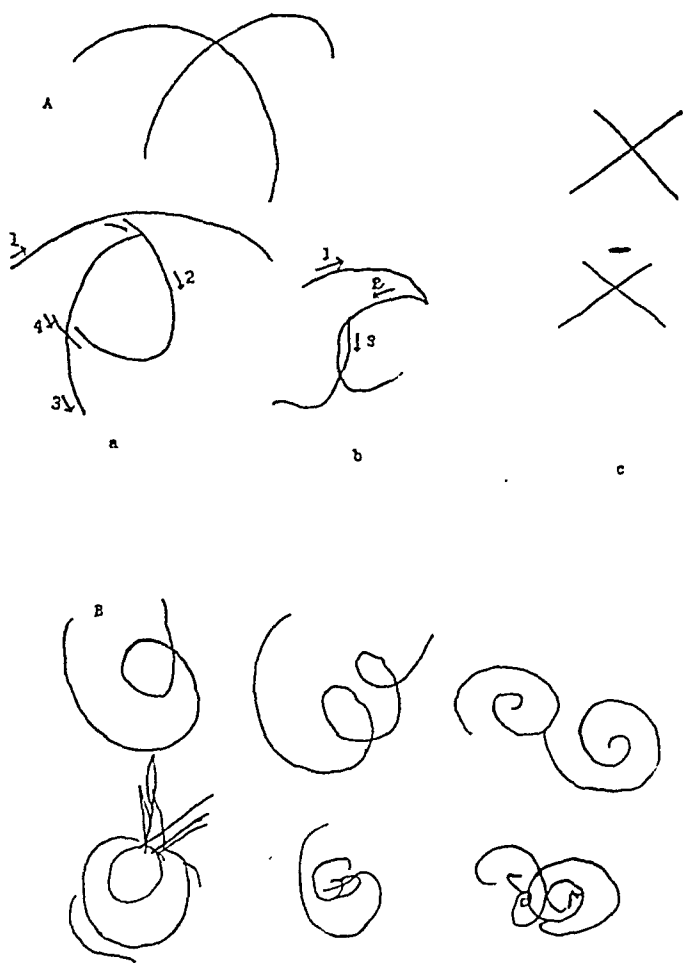
Fig. 6.—*A*, attempts to copy pattern (at top). Sequence and directions are indicated by numbers and arrows. Note disintegration of the figure on two consecutive attempts (*a* and *b*) when *c* was slightly curved. Date: April 15, 1943.

B, attempt to copy a pattern (at top). Note disintegration of the figure into several incoherent parts. Date: March 18, 1943.

when a cross was only slightly varied by curving the lines. More complicated figures made the confusion worse (fig. 6 *B*).

The patient's disturbance is strikingly evidenced by her inability to copy simple block designs. When she tried to copy a red rectangle surrounded by a white background with the Kohs blocks two months after injury (fig. 7), she started with a white block, then put a red one on its right side, lower than the white one, and then became thoroughly confused as to where to put the next one. Four months after injury she remarked, while practicing with the blocks, "The white baffles and confuses me. I always think there is something in addition," and pointed to the white background on the left of the sample. Thus she showed good insight into the so-called disturbance of figure-ground relationship. The background on the left interfered with her attention for the important figure in a way which had been noted before in her reading,
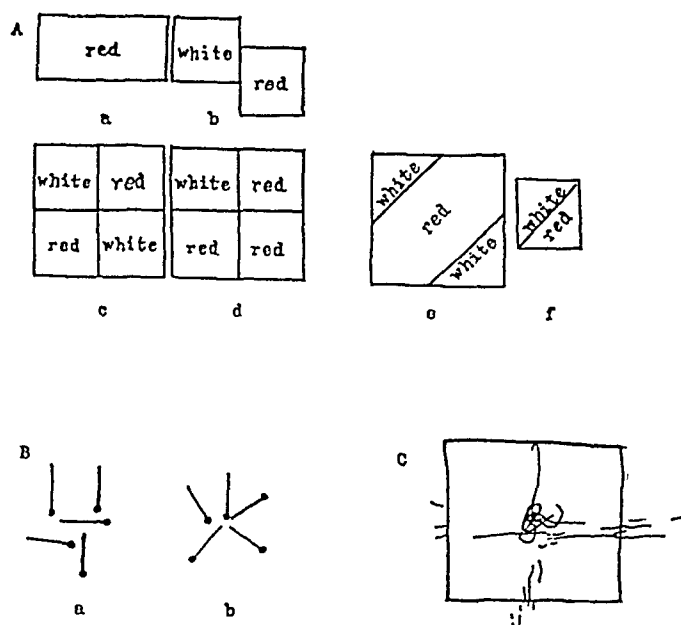
Fig. 7.—*A*, reproduction of Kohs block patterns, in which *a*. *c* and *e* are the samples and *b*, *d* and *f* are block reconstructions by the patient. Dates: Reconstruction *b* was done in January 1943, and *d* and *f* were made in May 1943.

B, pattern of matches (*a*), which the patient tried to copy (*b*). Date: May 27, 1943.

C, patient's attempt to mark the center of a square by drawing lines across and marking their crossing point. Date: Jan. 15, 1943.

when previous optic impressions interfered with subsequent ones. At present, seven months after injury, her copying of block designs has not improved much as compared with earlier attempts (fig. 7 *A*, *c*, *d*, *e* and *f*).

Agnostic patients copy patterns made of matches more easily since they can best perceive straight lines. Therefore the match test, although advocated by some authors, is more useful with apractic than with agnostic disturbances. The patient could copy simple patterns correctly but erred with more complicated ones (fig. 7 *B*).

Copying objects from life was easier for her than copying the same object from a drawing. She remarked, "Lines confuse me. If it is an object, I know which is front and which is in back."

Disturbance of Recognition of Spatial Relationships.—Although the patient was able to identify straight lines as such and to draw lines horizontally and vertically on request, she could not divide them correctly. During the first two months, when asked to divide a line in half, she traced several times along the line and marked the ends of the line over and over, sometimes somewhat beyond the original marks, before she made a dividing line. Thus she reenforced her knowledge of the length of the line by use of her proprioceptive sense. Whenever she is asked to divide a line in more than two parts, she still becomes confused. For instance, when asked to divide a line in three parts, she makes three dividing lines at random along the line and counts, "One, two, three." This is in keeping with her inability to divide by calculation. To comply with these tasks, simple as they may seem, the whole of the figure has to be registered as a visual image. This the patient is unable to do. The same difficulty applies when she is asked to mark the center of a circle or of a square (fig. 7 C). This she does by drawing diameters, and she marks the center at their crossing point.

She is able to differentiate between lines of different lengths and to judge distances roughly. For instance, when pins of different colors are stuck into a blotter 1 meter from her eyes, close to each other but not in the same line, the distance of each pin from her eyes being increased 1 cm., she is able to say which one is farther from her and which one nearer. She can also give a fair estimate of the length of larger objects. All this, however, implies a one dimensional procedure only, preponderantly that of addition. When she cannot apply this, she encounters difficulties. As one may expect, the patient also has difficulty in finding her way around in a new environment. When she returned home, after four weeks' stay in the hospital, she was at first unable to find her way around. During the first month she could not give any description of the streets in her immediate neighborhood, and she confused them during the following months. When she visits the hospital, where she has been many times, she still errs when taking turns in the corridors and has to look at the arrows to read directions. When she goes shopping she relies on certain marks, such as "a small white house at the corner where I have to make a turn," traffic lights and signboards.

VISUAL IMAGERY

Dreams.—It has been reported by some authors (Charcot,[13] Grünstein [14]) that their agnostic patients lost the ability to dream visually. Wilbrand [15] and Brain [16] each reported on an agnostic patient who had had an occasional visual dream which consisted of the patient's seeing only a single figure. The three dreams which this patient had lacked any clear visual component. While still in the hospital she dreamed that she was in an oxygen tent and that she had difficulty in breathing. She said that she had not actually seen anything but had heard the nurses talking to her. During her first two weeks at home she dreamed twice that she was still in the hospital, and woke up feeling relief at being at home. She does not remember having seen anything during these dreams. All this indicates that agnostic patients either have no visual dreams or that the visual component of their dreams is diminished.

Visualization and Formation of New Visual Images.—There is definite indication that this patient has not lost the ability to visualize or to form new visual images. However, this ability is defective. The impairment follows the rule of the rest of her disturbance. She has no difficulty in visualizing colors, but the difficulty grows on visualization of objects with more than one dimension. So, for instance, as late as six months after her injury, she visualized a bird as having four legs and a table as having two legs and made many similar mistakes. Occasionally, however, her formation of new visual images was surprisingly complete. For instance, eight weeks after her injury, and afterward, she gave correct, detailed descriptions of rooms visited by her recently.

DISTURBANCE OF ABILITY TO DRAW SPONTANEOUSLY

The patient's impairment of visualization and of optic imagery is exemplified by her spontaneous drawing. This ability was greatly impaired during the first two months but then improved steadily until the fifth month, after which it remained stationary. The disturbance is shown

13. Charcot, J. M.: Leçons sur les localisations dans les maladies du cerveau, Paris, V. A. Delahaye, 1882, vol. 3.

14. Grunstein, A. M.: Die Erforschung der Träume als eine Methode der topischen Diagnostik bei Grosshirnerkrankungen, Ztschr. f. d. ges. Neurol. u. Psychiat. 93:416-420, 1924.

15. Wilbrand, H.: Ein Fall von Seelenblindheit und Hemianopsie mit Sectionsbefund, Ztschr. f. Nervenh. 2:361-387, 1892.

16. Brain, W. R.: Visual Object-Agnosia with Special Reference to Gestalt Theory, Brain 64:43-62, 1941.

by a comparison of four drawings of the same object made at different times. Each time she was asked to draw a girl (fig. 8). Figure 8 *A* shows loss of awareness of bodily relations. On

Fig. 8.—(*A*) The "nostrils" are above the eyes and are surrounded by hair, evidence of interference of the previous drawing of the eyes. No mouth is indicated. The arms originate from the head. Date: Dec. 17, 1942.

(*B*) Two nostrils are drawn on the left, "one for each nostril"; the mouth (*1*) is below the chin. Date: Jan. 4, 1943.

(*C*) In drawing the nipples (*1* and *2*) the patient placed the right nipple (*2*) within the right arm. At last the patient was asked to draw the navel (*3*). Date: Jan. 25, 1943.

(*D*) No significant change from this drawing occurred subsequently. Fingers were not drawn at first. When asked to put them in, the patient did so, counting them out carefully. Date: April 15, 1943.

making the short lines around the "nostrils," she commented, that some people had hair about their nostrils. Immediately preceding this she had drawn the "eyes" without any eyelashes or eyebrows. This represents the same kind of interference of a previous optic performance on the subsequent one that had been encountered in her reading and in her block reconstructions— an optic perseveration, which may be misinterpreted as a "disturbance of figure-ground relationship." In figure 8 *C* a variation is made by addition of a "hat." She said, "That makes it

easier to draw the hair," but the drawing looks as if the hat was transparent. When asked to put the nipples in, she put the right one within the right arm (fig. 8 *C, 2*). She knew where to locate the nipples on her own body and had not intended to place a nipple on the arm, but she misinterpreted the right arm, although drawn by her a few minutes earlier, as a part of the trunk. After the fifth month her ability to draw a girl remained stationary (fig. 8 *D*).

Immediately after the patient had marked the navel (*3*) in figure 8 *C*, she was asked to draw a house (fig. 9). The resemblance to the drawing of a girl (fig. 8 *C*) is striking. At last she put in the "entrance" (fig. 9, *1*) and said, "The door is too high up. One would not be able to get in. I was thinking of the girl . . . the navel." Thus the patient showed considerable insight into her disturbance, which caused an interference of previous optic performance with subsequent ones.

The patient is able to locate correctly touch or pain stimuli applied to her body. This corresponds to her intact senses of touch, pain and proprioception. But she is unable to mark the location of the stimulus correctly on a chart of the body, since she lacks optic recognition of bodily relations. For instance, a circle was drawn which was to represent the contour of a face, and she was asked to draw the eyes (fig. 10 *A*). She made first one in the center and then another on the right. Then she said, "That is wrong." She then made lines across the circle in order "to judge distances," as she said, and finally

Fig. 9.—Drawing of a house, made immediately after that of a girl (fig. 8 *C*), the influence of which is striking in this sketch. The entrance (*1*) was placed above the ground, and the patient, noticing the mistake, explained that she was thinking of the navel (*3*) of the girl in figure 8 *C*. Date: Jan. 25, 1943.

marked another eye on the left. When asked to draw the mouth, she marked two symmetric ones. The aforementioned errors indicate disintegra-

tion of awareness of spatial relations. Similar examples have been given by von Stauffenberg,[6] Engerth[17] and others. Such a disturbance in agnostic patients was named "constructional apraxia" by Kleist,[18] who defined it as a failure of spatial construction without apraxia of movement. But it seems misleading to call a disturbance which is so closely related to visual disorder "apraxia." The same holds true for the term "optic apraxia," which Poppelreuter[19] used for the disturbance of drawing in optic-agnostic patients.

A

B
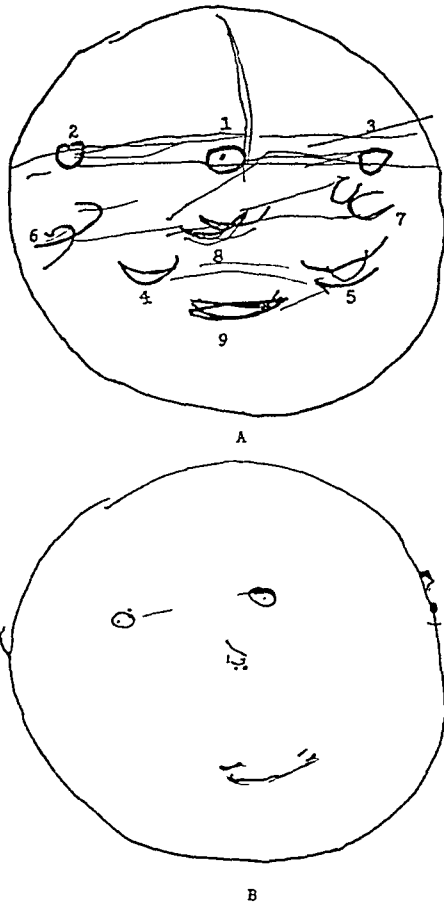
Fig. 10.—(*A*) The patient was asked to mark the eyes (*1, 2* and *3*) in the circle and then to mark the mouth (*4* and *5*). Noticing her error, she marked two ears on each side (*6* and *7*), then put the mouth in the center of the circle (*8*) and then placed it correctly (*9*). She made horizontal lines "to judge distances." Date: Jan. 11, 1943.

(*B*) Notable improvement five months later (June 18, 1943). The patient again made lines across the circle, as in *A*, but in doing so she seldom touched the paper.

17. Engerth, G.: Zeichenstörungen bei Patienten mit Autotopagnosie, Ztschr. f. d. ges. Neurol. u. Psychiat. **143**:381-403, 1933.

18. Kleist, K.: Gehirn-Pathologie, vornehmlich auf Grund der Kriegserfahrungen, Leipzig, Johann Ambrosius Barth, 1934.

19. Poppelreuter, W.: Zur Psychologie und Pathologie der optischen Wahrnehmung, Ztschr. f. d. ges. Neurol. u. Psychiat. **83**:26-152, 1923.

OBJECT AGNOSIA

Inanimate Objects.—During the first two weeks the patient did not recognize any objects. For instance, she called a comb "a fountain pen," scissors "a hair pin" and a little toy elephant "a pencil." After color recognition had returned, she guessed the identity of an object by its color. For example, at the end of the second week she called a dish of vanilla ice cream "scrambled eggs." She always tried to grasp the object, and she was usually able to identify it by touch. From the third week on she frequently traced around the object with her right index finger, a method similar to that used when she tried to read. At first she perceived the contours only. For example, during the second week she called a nickel and a round, silver compact each "a key ring." Identical responses of agnostic patients are reported all through the literature. For instance, Lissauer's[20] patient called a straw hat "a ring." After three weeks she began to fill in the contours, but she did not perceive the third dimension. So she called a square, white box "a piece of paper." During the second month she gradually became able to register the third dimension. This process of adding up visual impressions has, up to now, remained her way of recognizing objects by sight. At the time of the report, no deviation from the norm in the patient's way of recognizing objects would be noticed by the untrained observer, since her ability to guess and to add has improved notably. Her handicap, however, can still be brought out by tachistoscopic examination. Thus, during the fourth month, a green toy battleship, 4 inches (10 cm.) long, was shown to her at a gradually increased time of exposure. She gave the following responses:

1 sec.	"A fountain pen."
2 sec.	"A knife, green."
3 sec.	"A boat."

She commented: "At first I saw the front part. It looked like a fountain pen because it was shaped like a fountain pen. Then it looked like a knife because it was so sharp, but I thought it could not be a knife because it was green. Then I saw the spokes and that it was shaped like a boat, like in a movie where I had seen boats. It had too many spokes to be a knife or a fountain pen." She also called a piece of white soap "a piece of paper" after looking at it for one second, but she identified it correctly after two seconds. Consequently, the time which she requires adds up to such an extent that her relatives think she has become "very slow."

20. Lissauer, H.: Ein Fall von Seelenblindheit nebst einem Beitrag zur Theorie derselben, Arch. f. Psychiat. **21**:222-270, 1890.

Since this condition has not improved within the last few months, one may anticipate that the patient will continue to recognize by adding up parts instead of by simultaneous perception of all the parts for some time to come, if not permanently.

Animate Objects.—During the first weeks following injury the patient was unable to recognize people by sight. She did not even recognize her husband when he visited her for the first time, one week after her admission, but she identified him when he took her hand in his characteristic way. She was also keen in recognizing voices and footsteps. However, up to the present she has not been able to recognize people when she sees them for the first time after her injury, even though she had known them well. Only after they have made themselves known to her does she recognize them, and she then is able to recognize them at · later meetings. This shows that the patient must form new visual images and evidently has learned roundabout ways of recognition. This she does whenever she has considerable interest in a person. She does not recognize people whose conversation and personality are unessential to her, even if she has met them several times. On the other hand, she recognized a physician who had impressed her by a careful examination when she saw him for the second time in an elevator, although he did not recognize her. The patient trains herself to remember eyes, profiles, height and hair of different people. She is greatly helped by remembering voices and by anticipating whom she may meet. That the localization of the lesion within the occipital lobes may be correlated with a difference in impairment in recognition of animate and inanimate objects has been discussed by Nielsen and Sanborn [21] and by Olsen.[22] In this patient the disturbance in recognition of animate objects paralleled that of inanimate objects.

PICTURE AGNOSIA

The patient has more difficulty with the recognition of pictures than of objects. Colored pictures are recognized more easily than uncolored ones because in the former the details are impressed by the difference in color. Up to the present she has described pictures as children do, by enumerating details, one after the other. During the first two months she

recognized only a few items out of the whole picture. Thus, her reaction to two colored pictures,[11] presented to her one month after injury, the first picture consisting of a boy admiring a sailboat in a toy shop, the second showing the same boy bent down over the sailboat, playing with it in a pool, was as follows: The patient pointed to the boy in each picture and said, "A boy." When asked whether it was the same boy, she answered in the negative. The different posture of the boy changed the visual impression made on the patient. She then pointed to the boat in each picture and identified it as such, but she did not recognize it as the same boat and said, "It has a different color," pointing to the waves and ripples at the left of the sail boat, which impressed her as a part of the boat. This could be interpreted as a "disturbance of figure-ground relationship." However, the analysis of previous errors has shown that such a disturbance was simulated by the patient's adherence to earlier optic impressions. She still misinterprets black and white drawings to a considerable extent but she recognizes most of the details in colored pictures and adds them up. Her difficulty is greatest if recognition of a plurality of details is necessary for the understanding of the picture because, when faced with many items, she always overlooks some. The name "simultanagnosia" has been given by Wolpert [23] to the disturbance in patients who perceive only parts of the whole picture. However, the symptoms in his, and in similar, cases, as well as in this case, indicate that such a disturbance is never confined to the recognition of pictures but that it is present in all optic recognition. The term "simultanagnosia" would be appropriate for this patient's condition except that this term is restricted by definition to the agnosia of pictures.

This disturbance also prevents the patient from enjoying a moving picture. Whenever the picture shows crowds, as in a battle or during a dance scene, the patient cannot understand what is going on. She enjoys, however, scenes which are carried by one or two actors only. The accompanying voices and her observation of movements contribute to her understanding.

A striking observation, which has been reported in similar cases (Lissauer,[20] von Stauffenberg,[6] Heidenhain [7]), was made when objects or pictures which the patient had not been able to recognize were shown to her again later. In several instances she quickly stated that they had already been shown to her. This proves that the patient formed and stored visual images out of incomplete or erroneous visual impressions.

21. Nielsen, J. M., and Sanborn, A. L.: Agnosia for Animate Objects, Bull. Los Angeles Neurol. Soc. **7:** 102-104, 1942.

22. Olsen, C. W.: Mind-Blindness: Clinical and Pneumencephalographic Study of a Case of Infarction of the Brain, Bull. Los Angeles Neurol. Soc: **7:**43-47, 1942.

23. Wolpert, I.: Die Simultanagnosie-Störung der Gesamtauffassung, Ztschr. f. d. ges. Neurol. u. Psychiat. **93:**397-415, 1924.

ACALCULIA

In the beginning the patient was unable to calculate. She could count forward, but she made mistakes when counting backward. After two months she was able to count backward without mistake and to add and substract orally, but she could multiply only when the result was below 20. During the first four months she confused multiplication, substraction and addition, as well as the corresponding symbols. For instance, four months after injury, when asked how much was 9 times 7, she said, "Nine and 9 is 18 . . . and 7 . . . that would be 16." When it was repeated that she should multiply, not add, she succeeded in giving the right answer by reciting the multiplication table for 7 up to 63. At present, she is able to multiply all the digits correctly, but it is still almost impossible for her to do any dividing. Other methods of calculation are derived from adding, which was the patient's best ability. For dividing, however, one needs visualization of the whole that is to be divided. This causes unsurmountable difficulties for this patient, as well as for patients with a similar disturbance (see patient of Goldstein and Gelb [4]). The following responses were given during the fourth month of her illness:

63 divided by 9? "That is taking away, isn't it?" When it was repeated that she should divide, she said, "I forgot how you divide."

10 divided by 5? "That would be 50 . . . 5 . . . I mix it up with multiplication. Four 5's are 20. Wouldn't that make 5?"

6 divided by 3? "Dividing or taking away? Is it 9? 3?"

4 divided by 2? "That's 2. Two plus 2 is 4. You just take 2 away."

From now on the patient was instructed to practice dividing daily. The result was that she was able to remember some simple divisions for a while. But when practice was stopped, she forgot after a few days what she had remembered mechanically.

After she was able to recognize numbers by sight, she could read up to four digits correctly. But here, too, she does not perceive the number simultaneously but starts counting from the right to the left to find out its denomination. Anything beyond four digits causes unsurmountable difficulties. In the following sample is the patient's response six months after admission, when she was asked to read numbers:

4376 "1, 2, 3, 4." (The patient counted out the numbers 6, 7, 3, 4, according to their denomination.) When arrived at the 4, she said, "Four, that's thousand. Therefore, four thousand three hundred and seventy-six."

42179 "Four hundred and twenty-one thousand seventy-nine."

Thus, the patient just read one digit after the other without being able to make a proper division of the whole number.

After having been at first totally unable to tell the time, the patient worked out a system which is analogous to that reported for other patients with visual agnosia. Three months after injury, she reported: "I practice telling time. The 6 is below the 12 and the 9 across from the 3 on the watch. First I look for the hands to find which is the hour hand and which is the minute hand. Then I look for the numbers. I memorize that 1 means 5 minutes; 2, 10 minutes; 3, 15 minutes, and so on." Up to now, however, the patient confuses hour and minute hands and therefore makes mistakes. This difficulty is typical not only of agnostic but of aphasic patients (Head [5]). Normally, telling the time is done through simultaneous perception of the familiar sight of the watch, without the need of additional calculation.

The patient is able to say without hesitation which one of two numbers is greater, but she is unable to explain the difference in an abstract mathematical way. For example, when asked why 72 was more than 45, she said, "Because you can buy more for 72 cents than for 45 cents." Seemingly unessential variations of such a question confuse her. For instance, during the fourth month, she handled a problem as follows:

Which is more, four times 3 or six times 2? "Four times 3. Six times 2 is 18 . . . No, four times 3 is 18, Six times 2 is 12, so four times 3 would be more . . . No, 6 2's are 18 . . . No, 3 is more than 2. Therefore, four times 3 would be more than six times 2."

Thus, the two problems impose themselves on each other, and a separation of the whole problem into its proper parts proves to be impossible.

During the first month she was unable to indicate the number of days in a year or in a week. Ever since she has practiced this. But although she has improved, she is still not able to get it straight. Her estimation of time, for example, how many minutes had passed after she entered a room, does not seem to be impaired. Neither is her sense of rhythm, and she is good at imitating any rhythm that is tapped out.

Acalculia is present in all cases of pronounced optic-agnostic disturbance, in particular those with severe geometric-agnostic symptoms. It is also present, however, in cases of aphasia and apraxia. Consequently, the localization of lesions causing acalculia varies with different patients.

FINGER AGNOSIA

The patient is able to show, on request, any of her fingers. She does this by counting them

until she arrives at the one she is to show. If she is asked to name a finger on another person's hand or to show the same finger as that shown to her by another person, she first has to identify the thumb. If it is hidden, she is unable to recognize any finger. Patients with finger agnosia are usually able to recognize the first and the fifth finger. Since the contours of the first and the fifth finger are a continuation of those of the hand, the patient identifies them comparatively easily. Recognition of the second, third and fourth fingers by sight is difficult, since the patient cannot register their minute differences.

The finger agnosia of this patient is the same now as it was during the first weeks. She said herself: "If you show me all the fingers of your hand together and point to one, I can tell you which one it is because I can count. But if you show me only one and hide the others, I cannot make out which finger it is."

Such disturbances of awareness of bodily relations are usually accompanied by impairment in left-right orientation. This patient was unable to indicate left and right during the first two weeks. By the end of the third week, when asked about it, she invariably made the movement of writing with her right hand and said, "I write with this hand; therefore, this is the right one." At present; she still identifies right and left by "thinking."

Since its first description by Gerstmann,[24] finger agnosia has been observed to be associated with various lesions of the left hemisphere. Lange [25] differentiated finger agnosia caused by aphasic disorders from that due to apractic and agnostic disturbances. In the present case finger agnosia is a part of the optic-agnostic syndrome. A parallel can be drawn between this patient's finger agnosia and her visual alexia inasmuch as the patient cannot recognize the fingers on another's hand (impairment in reading), is unable to find out which of her own fingers corresponds to the one shown to her (impairment in copying) but on command can show her own fingers correctly (preservation of writing).

SPECIAL TESTS

Electroencephalogram. — Electroencephalographic examinations,[26] done three weeks and four months after injury, revealed a "very low voltage record, no build-up with over ventilation, no slowing and no definite focus of abnormal activity. No marked difference was noted between the first and the second encephalogram."

Examination of Visual Acuity and of Visual Fields.—The disturbance of reading complicates the examination of visual acuity of optic-agnostic patients. The best method is to find the shortest distance necessary for the subject to count two or three dots, for instance, chalk dots on a blackboard, and to compare this distance with that required by an emmetropic person. When the patient was examined in this way, her visual acuity was normal. She was able to recognize letters of the smallest print when they were exposed close to her, a fact which also proves that her visual acuity is normal. However, when her vision was examined with the Snellen tables at a distance of 20 feet (6 meters), it was easier for her to recognize large letters than small ones. By this method of examination visual acuity is not, much above 20/70 for either eye. This apparent discrepancy, which has also been reported for other optic-agnostic patients (Goldstein and Gelb [4]), might be explained by the fact that the patient reads by tracing the contour of a letter. Such a procedure is more difficult if performed over long distances than at close range.

On examination of her visual fields the patient has difficulty in fixing one point and at the same time in watching for the approaching target. But she can accomplish the task if she is told from what direction she is to anticipate the target. The visual fields are then normal (fig. 11). There is perhaps a slight constriction of the right lower visual field for color, particularly in the right eye. If present, it is too small a variation to produce any recognizable, additional symptoms. Examination for perimacular amblyopia or scotomas gave negative results.

Wide Range Vocabulary Test.—Since the usual, widely used intelligence tests require intact visual perception, a routine evaluation would be misleading in the case of this patient. Therefore, only the wide range vocabulary test of C. R. Atwell and F. F. Wells, form B, was used. The patient's intelligence, in terms of this test, was at a 16 year level, which corresponds to high school performance. By the same test, the average adult score is 50, which means 50 correct answers to 100 questions. The patient's score was 65, and therefore somewhat above average.

ADAPTATION TO ORDINARY LIFE

After the initial confusion had passed, the patient gave to the inexperienced observer the

24. Gerstmann, J.: Syndrome of Finger Agnosia, Disorientation for Right and Left, Agraphia and Acalculia: Local Diagnostic Value, Arch. Neurol. & Psychiat. 44:398-408 (Aug.) 1940.

25. Lange, J.: Agnosien und Apraxien, in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1936, vol. 6, pp. 807-960.

26. Interpretation was made by Mrs. Erna L. and Dr. Frederic A. Gibbs.

impression of a normal person. However, her family is aware of several rather obvious disabilities. At home, four weeks after her admission, she confused the silver on the table. When getting dressed she had difficulties, confusing her underwear with her blouse and not getting her arms into the right sleeves. After the first three months these errors did not recur. Twice she fell down steps when descending, and she comments that she is likely to overlook steps. She has no difficulty in walking up. The same disturbance was reported by Wilbrand's agnostic patient.[15] The patient's reading difficulties prevent her from cooking, since she confuses the different ingredients marked by labels. When sewing, she misplaces the stitches and therefore has given it up after several attempts. She takes care of her laundry, but the result is poor because she misses soiled parts. She is able to iron material of simple geometric forms, such as handkerchiefs and towels, but with more

possible to conduct any ordinary conversation with her. She is reasonably concerned about her husband, who joined the Army in March 1943. Her logic is undisturbed, and she immediately notices absurdities which are purposely inserted into a conversation.

REEDUCATION

This patient's case offered a unique opportunity for study since it was possible to observe her from the beginning of her illness and to follow her course until, after about six months, her condition became stationary. Most of the patients reported on in the literature were examined either only during the initial stage or after a stationary condition had been reached. This holds also for the famous patient of Goldstein and Gelb,[4] who was not studied until a year after his injury. At that time, and thereafter, his condition greatly resembled the present condition of my patient. During the patient's
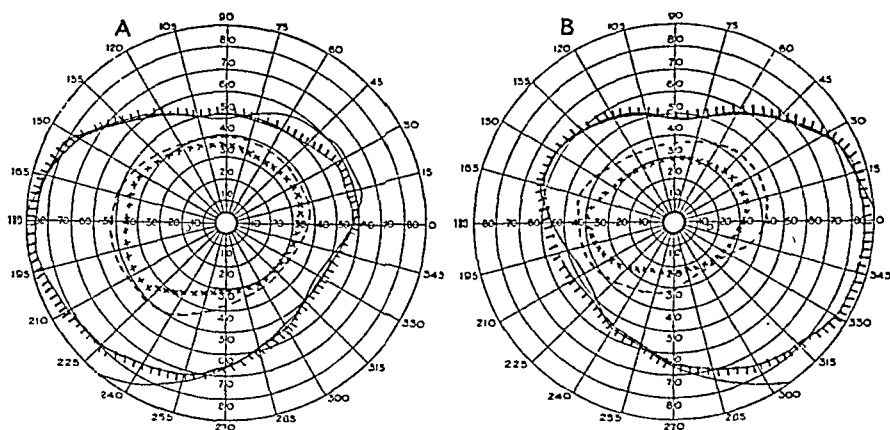
Fig. 11.—Visual fields for (*A*) the left eye and (*B*) the right eye. The fields for white are indicated by a line with hatching; the fields for blue, by a broken line, and the fields for red, by a line of crosses. Date, June 19, 1943; target, 1 degree.

complicated patterns she omits parts. For instance, recently she did not iron the collar on her blouse. When using the vacuum cleaner she omits sections of the rug. When crossing busy street intersections she frequently overlooks approaching cars because she perceives only parts of the whole situation. Consequently, she avoids such places, unless they are protected by traffic lights.

Several times a day she asks what time and what day it is. Her family is worried because she has lost the ability to attend to her financial affairs. She spends the money allotted to her on incidentals, instead of budgeting. This is in keeping with her impairment in calculation.

Apart from these obvious difficulties and her slowness, which is caused by her way of visual recognition, neither her family nor her friends notice any change in the patient's personality. She shows adequate affect and interest, and it is

period of rehabilitation she developed methods to compensate for her impairment of visual perception. She traces the contours of letters with her index finger in order to enforce visual perception and to replace recognition of the whole, which is denied her, by a substitute method of recognition, namely, that of adding up parts. She has trained herself to recognize letters by their outstanding characteristics, and she is still perfecting this. She uses "thinking," which consists of combining, anticipating and guessing, in order to make up for her disability, and she is keen in the use of touch, hearing, smell and taste during the process of recognition. She has formed new visual images which enable her to recognize people by a few outstanding characteristics. All these roundabout ways she found by herself in her struggle for readjustment. The question arises as to what can be done by others to help such patients. The course of recovery

of this patient indicates that the most important principle is not to interfere with improvisations, but to encourage them. There are limits to what can be overcome. For example, although the patient has learned to recognize simple patterns, she has made no progress in recognizing complicated ones. For a while efforts were made to improve her copying of complicated figures, with no success at all. In order that she hold what she has regained, continued practice is necessary. This can be seen from the fact that she began to confuse seldom used letters, such as q and z, after her condition had become stationary. Calculation, especially, has to be practiced since much of it becomes a matter of remembering mechanically if visualization is impaired. Continued supervision is advisable. Similar opinions have been expressed by Goldstein [27] and by Weisenburg and McBride.[28]

COMMENT

In all probability, the lesions in the brain in this case were the result of exposure to carbon monoxide fumes. Carbon monoxide was found in the blood of many victims of the Cocoanut Grove fire in amounts sufficient to kill. Although the Babinski reflex could be elicited initially in several patients, none of the other 131 patients who were admitted to the Boston City Hospital during the night of the disaster gave evidence of a permanent cerebral lesion. Only 1 other patient has sustained permanent neurologic damage. In this patient, 1 of the 39 admitted to the Massachusetts General Hospital (Cobb and Lindemann [29]), widespread damage both to the basal ganglia and to the white matter is assumed, which resulted in psychomotor, intellectual and aphasic disturbance.

Impairment of higher cortical function in survivors of carbon monoxide poisoning has been noted frequently. Visual agnosia in particular has been described in such patients by Schilder and Isakower,[30] Solomon [31] and Von Hagen.[32]

Lesions of the occipital lobe were stated to be present in all cases of visual agnosia in about 50 autopsy reports in the literature. Nielsen [33] and others pointed out that the lesion in the occipital lobe may be unilateral. In this case the lesion is probably bilateral, since lesions in the brain caused by carbon monoxide poisoning are usually symmetric and so little compensatory improvement occurred.

Different investigators (Henschen,[12] Kleist,[18] Nielsen and FitzGibbon,[1] Poetzl [2]) have attributed separate localizing significance to object agnosia, picture agnosia, geometric agnosia, acalculia, visual alexia and related symptoms. In view of the identity of mechanism exhibited by this patient for each of these disorders, the question may be raised whether the various symptoms may not be caused by the same lesion of the occipital or the occipitoparietal lobe, as proposed by Goldstein and Gelb.[4] On the other hand, no two patients with visual agnosia represent an identical picture. The intensity of the different symptoms varies, as does their accentuation. Difference in psychologic development of higher cortical function may account for this.

The present case offers the following advantages for study: The patient has sufficient, even somewhat above average, intelligence and considerable insight, so that she is able to furnish a great deal of information about the motives underlying her methods. She is only 22 years old, whereas most patients with similar disturbances were nearer 60. Brain [16] has given the only description of visual agnosia in a child. There is no accompanying aphasia or apraxia, which in the majority of cases confuses the picture. Though her initial confusion suggests the presence of multiple cerebral lesions at that time, the symptoms during the later stages conform to the syndrome of visual agnosia caused by occipitoparietal damage. Even during the first week of her illness the agnosia was limited to vision, whereas identification through other senses was intact. There is no impairment of visual acuity and no accompanying hemianopsia. Some authors (Brain,[16] Nissl von Mayendorf,[34] Poppelreuter [19]) have suggested that a patient's inability to perceive the whole might be caused by a defect in the visual fields and that this was the case in Goldstein and Gelb's [4] agnostic

27. Goldstein, K.: After Effects of Brain Injuries in War: Their Evaluation and Treatment, New York, Grune & Stratton, Inc., 1942.

28. Weisenburg, T., and McBride, K. E.: Aphasia, New York, Commonwealth Fund, 1935.

29. Cobb, S., and Lindemann, E.: Neuropsychiatric Observations, Ann. Surg. 117:814-824, 1943.

30. Schilder, P., and Isakower, O.: Optisch-räumliche Agnosie und Agraphie, Ztschr. f. d. ges. Neurol. u. Psychiat. 11:102-142, 1928.

31. Solomon, A. P.: Acalculia, Other Agnosias and Multiple Neuritis Following Carbon Monoxide Poisoning, M. Clin. North America 16:531-538, 1932.

32. Von Hagen, K. O.: Two Clinical Cases of Mind Blindness (Visual Agnosia), One Due to Carbon Monoxide Intoxication, One Due to Diffuse Degenerative Process, Bull. Los Angeles Neurol. Soc. 6:191-194, 1941.

33. Nielsen, J. M.: Unilateral Cerebral Dominance as Related to Mind Blindness: Minimal Lesion Capable of Causing Visual Agnosia for Objects, Arch. Neurol. & Psychiat. 38:108-135 (July) 1936.

34. Nissl von Mayendorf: Beiträge zur Lehre von der Seelenblindheit, Ztschr. f. d. ges. Neurol. u. Psychiat. 159:226-250, 1937.

patient. Goldstein[35] has presented evidence to disprove the validity of this opinion. That this is not necessarily so is also proved by the observations on this patient, as well as by those on other patients who had no defect in the visual field (Jossmann,[36] Wilbrand and Sänger,[37] Wolpert[23]). In addition, it has commonly been observed that a bilateral hemianopsic defect, sometimes with sparing only of macular vision, was not accompanied by any agnostic disturbance. Several such patients had learned to shift their maculas, and they traced the contours of the object with their heads. It may be that the constriction of the visual fields in the patient of Goldstein and Gelb[4] caused the peculiar tracing movements of his head, particularly since this symptom has not been observed in other agnostic patients with intact visual fields.

This patient's agnosia belongs to the "apperceptive" (which is the same as perceptive) type. Lissauer[20] described this disturbance as one resembling "the condition of a person whose optic impressions are limited to light and difference of colors but who no longer has any concept of forms and objects. . . . The recognition of the outer world is made impossible primarily because of insufficient perception." This type of agnosia can be separated from that of "associative" visual agnosia, which was also described by Lissauer.[20] Patients with the latter type of agnosia perceive forms correctly, or approximately correctly, but their perception has no meaning for them. A survey of the literature reveals that the majority of patients have a mixed type, presenting both apperceptive and associative disturbances. Conditions such as that of my patient, whose symptoms are predominantly caused by a disturbance of perception, are rare. The type of agnosia a patient presents is best indicated by whether he is or is not able to copy. If, like this patient, he cannot copy, he has a disturbance of perception. If he can copy, but cannot identify what he has copied, his disturbance is on a higher level and represents an impairment in association of visual perception with the optic image in the cortex.

In this patient recognition through simultaneous perception of all the parts has deteriorated into perception of parts. To achieve some recognition of the whole, she has to add up details,

thus requiring more time for recognition than is normal. In an attempt to shorten this procedure the patient resorts to guessing. Consequently, she frequently errs, if it is not possible to identify the whole from the parts she has perceived. The name "simultanagnosia" would be a good characterization of this disturbance, except that Wolpert[23] has reserved this term for inability to perceive the whole of a picture only.

Liepmann[38] compared the confusion experienced by agnostic patients with that of a normal person when he looks at concealed object pictures which to him give the impression of meaningless lines. Anticipation of what one may find helps to unravel the lines. In such pictures the "figure-ground relationship" has been artificially confused. Goldstein and Gelb[4] have suggested that a disturbance of this relationship is of fundamental importance in patients with lesions of the brain. Such a disturbance is also suggested by this patient's errors: She builds the white background into the block design when she is trying to copy a pattern, and she misinterprets pictures by confusing the background with the important figure. Especially when she is reading, previously seen words impose themselves on subsequent ones and interfere, regardless of whether these words have been recognized or not. All this shows that the patient is caught by previous optic impressions, which superimpose themselves on subsequent ones, with resulting misinterpretations. When adding up subsequent visual perceptions, the patient habitually proceeds from the left or above to the right or below, which is the direction of writing. Therefore, the visual impressions to which she adheres are mainly to the left and above. This perseveration of optic impressions and subsequent interference with visual performance is not a "disturbance of figure-ground relationship," although the patient's errors may suggest such an interpretation.

Visual agnosia is occasionally misinterpreted as "hysteria" by persons with no experience in this field. Like many organic diseases, visual agnosia, too, can be imitated by a functional disorder (Teitelbaum,[39] van Vleuten[40]). If repeated examinations can be made, it is not difficult to differentiate the organic from the functional condition, since all the errors associated with visual agnosia follow the same pattern. A clear indication that the disease is caused by

35. Goldstein, K.: Some Remarks on Russel Brain's Article Concerning Visual Object Agnosia, J. Nerv. & Ment. Dis. **98**:148-153, 1943.

36. Jossmann, P.: Zur Psychopathologie der optisch-agnostischen Störungen, Monatschr. f. Psychiat u. Neurol. **72**:81-149, 1929.

37. Wilbrand, H., and Sänger, A.: Die Neurologie des Auges, Wiesbaden, J. F. Bergmann, 1917, vol. 7, pp. 393-446.

38. Liepmann, H.: Ueber die agnostischen Störungen, Neurol. Centralbl. **27**:609-617, 1908.

39. Teitelbaum, H. A.: Psychogenic Body Image Disturbances Associated with Psychogenic Aphasia and Agnosia, J. Nerv. & Ment. Dis. **93**:581-612, 1941.

40. van Vleuten, C. F.: Funktionelle Seelenblindheit, Centralbl. f. Nervenh. u. Psychiat. **28**:49-64, 1905.

a lesion of the brain is the presence of optic perseveration, which is hardly ever observed with hysteria. Misinterpretations and conclusions arrived ·at by guessing are also more apt to occur in visual agnosia, since hysterical patients rarely misinterpret, but usually bluntly comment that they do not recognize what is shown them.

SUMMARY

A case of visual agnosia in a woman aged 22 has been described. the course of the illness having been followed from the first day until the condition became stationary. The patient is 1 of the 2 persons in whom permanent lesions of the brain were produced, probably by carbon monoxide fumes. in a fire disaster at a night club on Nov. 28, 1942.

The fundamental disturbance consists of the patient's inability to perceive the whole, the *Gestalt,* visually. Only parts of the whole are perceived, and their correct relation is not recognized. This results in an inability to read, to copy letters and geometric figures and to recognize pictures or objects on short exposure. Writing is unimpaired.

Owing to the patient's intelligence and insight into her disability, it was possible to identify an additional disturbance in the nature of a perseveration of visual attention and optic impressions. Preceding optic impressions superimpose themselves on subsequent ones, so that proper perception and recognition are interfered with. This symptom is of the same category as psychomotor perseveration and perseveration of speech and writing.

According to Lissauer's first description, such a condition belongs to the "apperceptive" type of visual agnosia, since there is a primary disturbance of optic perception. In this patient the disturbance is clearcut to an unusual degree. The identity of the mechanism exhibited by this patient in each of the disorders of visual performance makes it unlikely that the various symptoms of optic agnosia have a separate localizing significance.

Compensatory efforts to build up new methods of visual recognition should be encouraged. Constant practice is necessary, since such a patient is likely to distort and to forget what he has learned.

Harvard Medical School.

PSYCHOPHARMACOLOGIC STUDY OF SCHIZOPHRENIA AND DEPRESSIONS

INTRAVENOUS ADMINISTRATION OF SODIUM AMYTAL AND AMPHETAMINE SULFATE SEPARATELY AND IN VARIOUS COMBINATIONS

JACQUES S. GOTTLIEB, M.D.

IOWA CITY

AND

CAPTAIN FRANK E. COBURN

MEDICAL CORPS, ROYAL CANADIAN ARMY

The intravenous administration of sodium amytal has been employed in the study of various psychoses since the introduction of the method by Blackwenn [1] in 1930. He used the drug to produce rest and sleep, and on the patient's recovery from the narcosis he noted brief lucid periods. Lindemann [2] then demonstrated that similar, and equally prolonged, remissions could be produced by intravenous administration of the drug in doses which were insufficient to cause sleep. Striking changes were frequently produced in resistive and mute schizophrenic patients. Their attitude changed from that of resistiveness, withdrawal and seclusiveness to one of friendliness and emotional warmth. There were willingness to discuss personal problems and a desire to retain the condition produced by the drug. The structure of the delusional and hallucinatory systems was not altered, however—in contrast to the improvement in contact with the environment, with respect both to communication and to warmth of emotion.

Since its introduction sodium amytal administered intravenously in subnarcotic doses has been employed extensively for various purposes. It is helpful as a diagnostic tool, permitting clarification of the mental content and the structure of the illness. It therefore has value in differential diagnosis.[3] The total reaction frequently leads

to a revelation of hidden thoughts, which allows a search for and discussion of the patient's critical experiences and attitudes. It therefore is an aid in psychotherapy.[4] The type of response obtained in a schizophrenic patient is of assistance in evaluation of the prognosis. The more closely the patient's behavior approaches normal under the influence of the drug. the better the outlook.[5] Furthermore, it has value for investigative purposes, allowing psychometric and other studies of intellectual and emotional functions.[6]

Since the reaction of a psychotic patient to the intravenous injection of sodium amytal is of diagnostic, therapeutic, prognostic and investigative importance, attempts have been made to improve the response to this drug. Drowsiness and shortness of reaction frequently mask the desired effect. As a result, various stimulants of the central nervous system. such as caffeine and sodium benzoate,[7] metrazol [8] and amphet-

1. Blackwenn, W. J.: Narcosis as Therapy in Neuropsychiatric Conditions, J. A. M. A. **95**:1168 (Oct. 18) 1930.

2. Lindemann, E.: Psychological Changes in Normal and Abnormal Individuals Under the Influence of Sodium Amytal, Am. J. Psychiat. **88**:1083 (May) 1932.

3. Berrington, W. P.: Psycho-Pharmacologic Study of Schizophrenia, with Particular Reference to Mode of Action of Cardiazol, Sodium Amytal and Alcohol in Schizophrenic Stupor, J. Ment. Sc. **85**:406 (May) 1939. Sullivan, D. J.: Psychiatric Uses of Intravenous Sodium Amytal, Am. J. Psychiat. **99**:411 (Nov.) 1942.

4. Wagner, C. P.: Pharmacological Action of the Barbiturates: Their Use in Neuropsychiatric Conditions, J. A. M. A. **101**:1787 (Dec. 2) 1933. Longpre, F.: Sodium Amytal Combined with Psychotherapy in Non-Cooperative and Cataleptic Patients, Massachusetts Dept. Ment. Health, Symposium on Therapy, 1939, p. 5.

5. Gottlieb, J. S., and Hope, J. M.: Prognostic Value of Intravenous Administration of Sodium Amytal in Cases of Schizophrenia, Arch. Neurol. & Psychiat. **46**:86 (July) 1941.

6. Layman, J. W.: A Quantitative Study of Certain Changes in Schizophrenic Patients Under the Influence of Sodium Amytal, J. Gen. Psychol. **22**:67 (Jan.) 1940.

7. Broder, S. B.: Therapy in Catatonia: Effects of Combining Caffeine Sodium Benzoate with Sodium Amytal, Am. J. Psychiat. **93**:957 (Jan.) 1937.

8. Reitman, F.: Some Observations on Sodium Amytal Experiments: Preliminary Report, J. Ment. Sc. **87**:96 (Jan.) 1941.

amine sulfate,[9] have been employed in an attempt to improve the type of response, to decrease drowsiness and to prolong the reaction.

Our purpose in this study was to evaluate the psychologic effects of combined intravenous injections of sodium amytal and amphetamine sulfate in patients with schizophrenia or depressions. In preliminary studies on selected subjects, i. e., patients with schizophrenia who were mute, resistive and in poor contact with the environment and patients with depressions of various types, there were apparent improvement of response, diminution of drowsiness and prolongation of the desired effect. The fact, however, that amphetamine sulfate combined with sodium amytal seemed to improve the response in selected patients is not necessarily assurance that the same effect will be obtained in all patients with similar disturbances. A "good" response to the intravenous injection of sodium amytal, for instance, occurred in 15 of 100 schizophrenic patients tested, an incidence of only 15 per cent.[5] The present study, then, was designed to evaluate the psychologic responses produced by various combinations of these two drugs in typical patients with schizophrenia or depression. No effort was made to report the physiologic responses, as they were qualitatively consistent with those reported by Myerson and his associates.[10]

METHOD

Twenty consecutive patients [11] admitted to the hospital who were suitable for testing, 10 of whom had schizophrenia and the other 10 depressions, were subjected to the following routine procedure:

On five successive days the patient was given one of a series of intravenous injections of the drugs early in the morning, the type and duration of the response and the degree of narcosis being noted. The doses of the drugs were always the same: 250 mg. of sodium amytal and 10 mg. of amphetamine sulfate. In the first injection sodium amytal alone was given; in the second, amphetamine sulfate; in the third, sodium amytal followed immediately by amphetamine sulfate; in the fourth, amphetamine sulfate followed by sodium amytal, and in the fifth, a mixture of sodium amytal and amphetamine sulfate. This procedure was selected because we were interested in a comparison of the reactions of the patient rather than in obtaining the best responses possible by variations in the doses of

9. Myerson, A.: The Reciprocal Pharmacological Effects of Amphetamine (Benzedrine) Sulfate and the Barbiturates, New England J. Med. **221**:561 (Oct. 12) 1939.

10. Myerson, A.; Roman, J.; Rinkel, M., and Lesses, M. F.: The Effect of Amphetamine (Benzedrine) Sulfate and Paradrine Hydrobromide on Sodium Amytal Narcosis, New England J. Med. **221**:1015 (Dec. 28) 1939.

11. Schizophrenic patients who showed no response to sodium amytal were omitted from this study, for obvious reasons. One patient with a depression was omitted from the study because of an atypical response.

the drugs. Except for the tolerance built up to the barbiturate, the preliminary studies indicated that the order in which the combined drugs were given was immaterial.

The reactions were evaluated as good, moderately good and poor. For the patient with schizophrenia, a good reaction was defined as one in which the affect was warm and appropriate to the thought content, the associations normal and the insight good so far as the patient recognized that he was ill. A moderately good reaction was defined as improvement in affect, associations and insight with persisting evidence of abnormalties. A poor reaction was defined as considerable defect in affect and thinking or as failure to respond.

For the patient with a depression a good reaction was defined as a shift of the affective state to or nearly to the normal level and, at the same time, disappearance of all evidence of retardation or agitation, whichever was present. A moderately good reaction was one in which there were definite improvement in the affective state and diminution of retardation or agitation but abnormalities were still evident. A poor reaction was characterized by no significant change in any of the symptoms or by complete failure to respond.

RESULTS

In table 1 are presented the duration and type of response elicited by the various combinations of the two drugs in the 10 depressed patients. The duration of the response was determined to the nearest half-hour. The reactions to the initial injection of sodium amytal were good in 3 patients, moderately good in 4 patients and poor in 3 patients. The average duration of the response was two and four-tenths hours. The intravenous injection of 10 mg. of aphetamine sulfate produced mildly increased tension, tearfulness and agitation in 3 patients and no response in 7 patients. When injection of sodium amytal was followed immediately by injection of amphetamine sulfate, 1 patient had a good reaction and 9 patients moderately good reactions. The average duration of the response was five and eight-tenths hours. When amphetamine sulfate was followed by sodium amytal, 1 patient had a good reaction, 6 moderately good reactions and 3 poor reactions. The average duration of the response was three and twenty-five–hundredths hours. When sodium amytal and amphetamine sulfate were injected together, 1 patient had a good response, 6 moderately good responses and 3 poor responses. The average duration of the response was five and six-tenths hours.

In summary, the psychologic characteristics of the reactions were not significantly changed for the group of depressed patients by the addition of amphetamine sulfate to the sodium amytal, but the duration of the response was increased. The narcotic effects were somewhat less prominent. From this table it appears that the longest reactions were obtained when the two drugs were given in mixture or the sodium amytal was given

first. There were of course exceptions to the general rule, as evidenced in case 6, in which the initial reaction to sodium amytal alone was as long as any of the subsequent reactions.

average duration of the response was three and nine-tenths hours. To amphetamine sulfate given alone there were failure of response in 6 patients and slight changes, characterized by increased.

TABLE 1.—*Responses of Patients with Depressions to Sodium Amytal and Amphetamine Sulfate Alone and in Combinations*

Case No.	Diagnosis *	Sodium Amytal, 250 Mg.		Amphetamine Sulfate, 10 Mg.		Sodium Amytal Followed by Amphetamine Sulfate		Amphetamine Sulfate Followed by Sodium Amytal		Sodium Amytal and Amphetamine Sulfate Together	
		Response	Duration, Hr.	Response	Duration, Hr.	Response	Duration, Hr.	Response	Duration, Hr.	Response	Duration, Hr.
1	M. D. D.	Good	1½	Tense; tearful; agitated	4	Moderately good (drowsy)	5	Moderately good (drowsy)	2½	Poor (drowsy)	5½
2	M. D. M.	Good (drowsy)	4	None	0	Moderately good (drowsy)	6½	Moderately good (drowsy)	6	Poor	5
3	M. D. P.	Good	6½	None	0	Good	9½	Good	5½	Good (sleepy)	12
4	I. M.	Poor (drowsy)	½	Slightly restless	½	Moderately good	7½	Poor	0	Moderately good	10½
5	M. D. D.	Moderately good (sleepy)	½	None	0	Moderately good	2½	Moderately good (drowsy)	2½	Moderately good	1½
6	M. D. D.	Moderately good	2½	Tearful; agitated	1½	Moderately good (drowsy)	½	Moderately good	2½	Moderately good	1½
7	M. D. D.	Poor (sleepy)	½	None	0	Moderately good (sleepy)	12	Moderately good (sleepy)	6	Moderately good (sleepy)	6
8	I. M.	Moderately good (sleepy)	1	None	0	Moderately good	1½	Poor	2	Moderately good	2
9	I. M.	Poor (sleepy)	1½	None	0	Moderately good	9	Poor (sleepy)	2	Poor (sleepy)	4
10	M. D. D.	Moderately good	5½	None	0	Moderately good	4	Moderately good	3½	Moderately good	8
	Average		2.4				5.8		3.25		5.6

* M. D. D. indicates manic-depressive psychosis, depressive type; M. D. M., manic-depressive psychosis, mixed type; M. D. P., manic-depressive psychosis, perplexed type, and I. M., involutional melancholia.

TABLE 2.—*Responses of Patients with Schizophrenia to Sodium Amytal and Amphetamine Sulfate Alone and in Combinations*

Case No.	Type of Schizophrenia	Sodium Amytal, 250 Mg.		Amphetamine Sulfate, 10 Mg.		Sodium Amytal Followed by Amphetamine Sulfate		Amphetamine Sulfate Followed by Sodium Amytal		Sodium Amytal and Amphetamine Sulfate Together	
		Response	Duration, Hr.	Response	Duration, Hr.	Response	Duration, Hr.	Response	Duration, Hr.	Response	Duration, Hr.
1	Paranoid	Good (sleepy)	3½	None	0	Moderately good	2½	Poor (drowsy)	6½	Moderately good (drowsy)	4
2	Paranoid	Moderately good (drowsy)	4	None	0	Moderately good	2	Poor	1½	Moderately good	3
3	Hebephrenia	Good (drowsy)	½	None	0	Good	4	Poor	3	Moderately good	5
4	Undifferentiated	Good	1	None	0	Good	6	Good	2	Good	3½
5	Hebephrenia	Good	7½	Tense; restless	½	Moderately good	1½	Moderately good	1½	Moderately good	1¼
6	Undifferentiated	Moderately good	5½	None	0	Moderately good (drowsy)	2	Moderately good	3	Moderately good (sleepy)	5½
7	Hebephrenia	Good (sleepy)	5½	Tense; tearful	½	Moderately good	7	Moderately good	10	Good	7
8	Hebephrenia	Poor (sleepy)	4½	None	0	Moderately good	2	Poor (drowsy)	9	Moderately good (drowsy)	3
9	Undifferentiated	Moderately good (sleepy)	5	Tense; restless	1	Moderately good	2	Moderately good	8½	Moderately good (drowsy)	5
10	Paranoid	Poor (drowsy)	2	Agitated; depressed	2	Poor	2	Poor	½	Poor	1½
	Average		3.9				3.1		4.55		3.9

In table 2 are presented the psychologic effects in 10 schizophrenic patients of sodium amytal and amphetamine sulfate, given separately and in various combinations. To sodium amytal alone 5 patients gave a good reaction, 3 moderately good reactions and 2 poor reactions. The

talkativeness, restlessness and tension, in 4 others. When sodium amytal was followed by amphetamine sulfate, 2 patients gave good reactions, 7 moderately good responses and 1 a poor response. The average duration was three and one-tenth hours. When amphetamine sulfate was

followed by sodium amytal, 1 patient gave a good reaction, 4 moderately good reactions and 5 poor reactions. The average duration was four and five-tenths hours. When the two drugs were given together, 2 patients gave good responses, 7 moderately good responses and 1 a poor response. The average duration was three and nine-tenths hours.

In summary, then, of the psychologic responses of the schizophrenic patients, the initial injection of sodium amytal alone produced the best, while injection of amphetamine sulfate followed by that of sodium amytal gave the poorest. The duration of the response when amphetamine was added to the amytal was increased for 4 of the 10 patients, was not significantly changed for 2 patients and was shorter for 4 patients. In most instances, however, the addition of amphetamine sulfate removed in part the narcotic effects of the sodium amytal. The average duration of the responses with the various combinations of the two drugs was approximately the same as that for the sodium amytal alone.

COMMENT

The data indicate that the addition of amphetamine sulfate to sodium amytal injected intravenously in patients with depressions does not change significantly the psychologic response to the drug except for dissipation of drowsiness to some degree and increase in duration of the effect. Furthermore, the best responses were obtained when the two drugs were given as a mixture or the amytal was injected first. In contrast, the schizophrenic patients showed on the average the same length of response, a slightly poorer psychologic reaction and a lessening of drowsiness. For individual patients the duration of the responses was increased. Other patients gave responses which were shorter. This may have been due to the observed phenomenon that subsequent responses to sodium amytal in schizophrenic patients often become poorer—indeed, sometimes they may fail to appear at all.[12] This is consistent with the tolerance which is known to develop to drugs of the barbiturate group.[13] Such tolerance, however, was not observed in the patients with depressions.

SUMMARY

A study of the psychologic effects in 10 patients with schizophrenia and in 10 patients with depressions of intravenous administration of sodium amytal and amphetamine sulfate alone and in various combinations revealed that the addition of the amphetamine diminished the drowsiness of both groups of patients and lengthened the response of the depressed patients.

Iowa State Psychopathic Hospital.

12. Unpublished data.

13. Tatum, A. L.: The Pharmacology of Barbiturates, in Luck, J. M., and Hall, V. E.: Annual Review of Physiology, Stanford University, Calif., Annual Reviews, Inc., 1940, vol. 2.

SITE OF ORIGIN OF FASCICULATIONS IN VOLUNTARY MUSCLE

FRANCIS M. FORSTER, M.D., AND BERNARD J. ALPERS, M.D.

PHILADELPHIA

Involuntary contractions of groups of muscle fibers apparent through the intact skin, and known as fasciculations, have long been considered as evidence of disease of the anterior horn cells. This opinion has resulted from their appearance in cases of disease involving the anterior horn cells. The increase of fasciculations produced by prostigmine and some of the observa-

Fig. 1.—Sample tracings taken during a control period (1) and during periods of spinal anesthesia (2) and peripheral nerve block (3) demonstrate no significant change in the number of fasciculations. The horizontal marker indicates an interval of one second; the vertical marker, an amplification of 50 microvolts.

tions reported on the effect of nerve root and peripheral nerve block cast doubt on the central origin of these involuntary movements. These investigations were undertaken to determine the site of origin of fasciculations.

METHOD

Four patients were studied, 3 of whom had amyotrophic lateral sclerosis. The remaining patient had pronounced fasciculations, weakness and atrophy as residuals of acute infectious polyneuritis. Restless and poorly cooperative patients were not included in these studies, for by their automatic and voluntary movements the incidence of fasciculations would have been increased and inclusions of data for periods in which movement was not possible, such as those of nerve block and spinal anesthesia, would have resulted in a false and misleading reduction in the incidence of fasciculations. By the careful placing of extremities during the recording, postural movements were reduced to a minimum.

All records were taken by a three channel, condensor-coupled amplifier with an ink-writing oscillograph (Grass). The electrodes employed were coaxial needles, two small needles placed in the muscle 1 cm. apart and two solder disk electrodes similarly placed over the skin. All records were bipolar. Throughout a single experiment the electrodes were left in place. Prior to

From the Department of Neurology Jefferson Medical College of Philadelphia.

the administration of a drug or the carrying out of a procedure a control record of twenty to thirty minutes was obtained. The effect on the incidence of fasciculations was determined for the following agents: Prostigmine, acetylcholine and mecholyl, given intramuscularly; curare, administered intravenously; spinal anesthesia, and peripheral nerve block. The effects of the prostigmine and mecholyl were studied during spinal anesthesia, peripheral nerve block and curarization. The recorded frequencies of fasciculations throughout each of these experiments were charted for each patient.

RESULTS

During spinal anesthesia the diphasic spikes associated with fasciculations were as prevalent as those appearing during the control period (figs. 1 and 3). Injection of procaine into the common peroneal nerve, resulting in paralysis, did not alter the frequency of fasciculations in the paralyzed muscles (figs. 1 and 4). The administration of prostigmine during spinal anesthesia (fig. 3) or peripheral nerve block (fig. 4) resulted in a notable increase in the number of fasciculations in the paralyzed muscles, comparable to the response to prostigmine without previous spinal anesthesia or nerve block.

Curarization resulted in the abolition of fasciculations (figs. 2 and 5). To obtain this result it was not necessary to carry curarization to the point of motor paralysis. Voluntary movement during partial curarization resulted in the usual burst of muscle spikes. These bursts were not followed by fasciculations, as was usually observed in control periods. The administration of
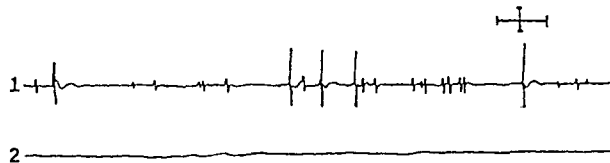
Fig. 2.—Sample tracings during a control period (1) and during a period of curarization (2) demonstrate the abolition of fasciculations by curarization. The values for time and amplification are the same as those indicated in figure 4.

prostigmine during curarization failed to induce fasciculations (fig. 5).

Mecholyl in doses sufficient to produce systemic symptoms had no effect on the incidence of fasciculations during control states, spinal anesthesia, nerve block or curarization.

264
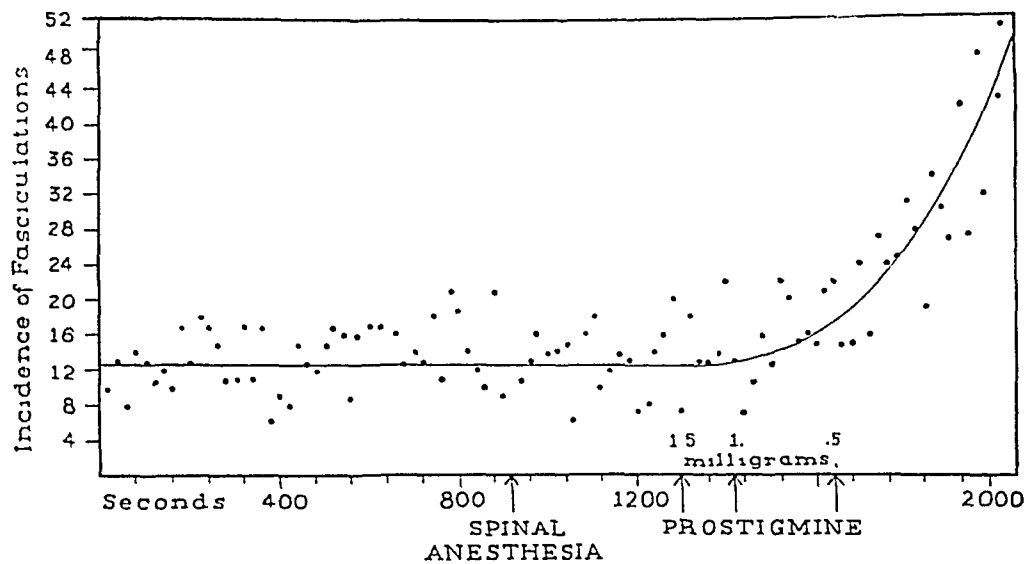
Fig. 3.—Chart showing the frequency of fasciculations during a control period and during spinal anesthesia. The incidence of fasciculations is plotted for consecutive twenty second intervals. The chart demonstrates no change in frequency of fasciculations during spinal anesthesia alone but a striking increase after administration of prostigmine during spinal anesthesia.
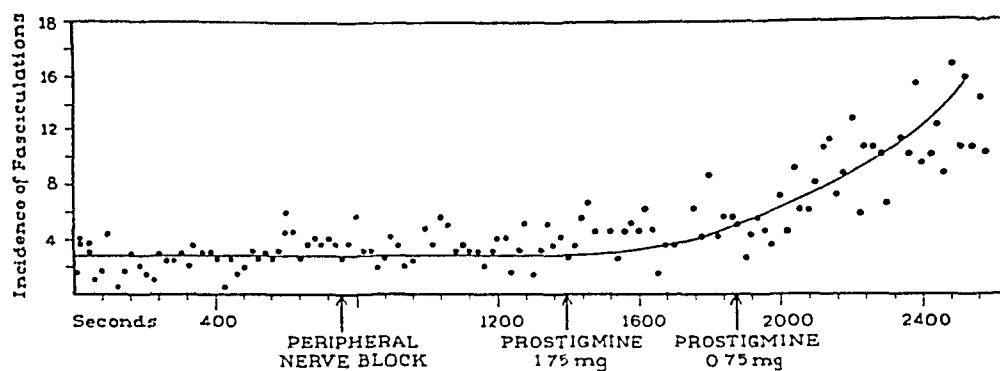
Fig. 4.—Chart showing the frequency of fasciculations during a control period and during peripheral nerve block (common peroneal nerve). The incidence of fasciculations recorded from the tibialis anticus muscle is plotted for twenty second intervals. The chart demonstrates no change in frequency of fasciculations during peripheral nerve block, but administration of prostigmine during such block resulted in a striking increase.
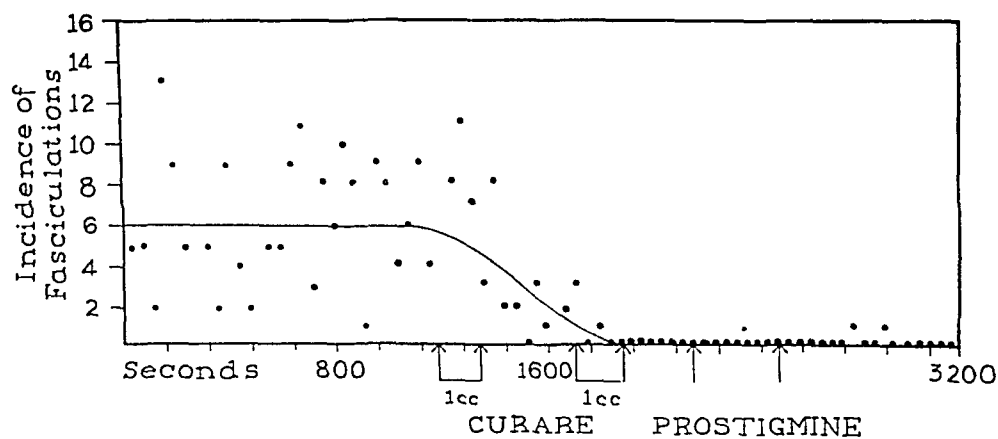
Fig. 5.—Chart showing the frequency of fasciculations during a control period and during curarization. The incidence of fasciculations was recorded at forty second intervals. The chart shows the abolition of fasciculations produced by curarization and the failure of prostigmine to induce their reappearance.

COMMENT

Since muscular fasciculations are most commonly observed with disease of the anterior horn cells, they have come to be considered as evidence of destruction of these neurons. The observations of Langley and Kato[1] that physostigmine produces fasciculations have been frequently confirmed, and prostigmine has been shown to have a similar effect. The action of these drugs is known to be due to the preservation of acetylcholine at the myoneural junction, since the characteristic response to administration fails when acetylcholine is absent, as in chronic denervated preparations. Langley and Kato also demonstrated that curare abolishes the fasciculations produced in animals by physostigmine. The effect of prostigmine and physostigmine on fasciculations was the first indication that fasciculations might arise wholly or in part at the myoneural junction. The only evidence of pathologic change at the myoneural junction in progressive muscular atrophy is the as yet unconfirmed observations of Pommé and Noël.[2] These authors described a decrease in the number of plate granules in the sole.

Denny-Brown and Pennybacker[3] differentiated between the constant irregular tremor of exposed denervated muscle and the coarse involuntary muscular twitching apparent through the skin. The former they called fibrillation; the latter, fasciculation. They expressed the opinion that fibrillations are due to sensitization of the degenerating muscle to the small circulating amounts of acetylcholine, and that fasciculations arise from a pathologic process either in the anterior horn cell or in the peripheral nerve; in view of the pathologic evidence, they suspected the anterior horn cell. Their conclusion as to the origin of fasciculations was based on their observations of single contractions in fixed groups of muscle fibers and was supported by the presence of a recurrent pattern, i. e., the repetition of a certain combination of spikes at definite intervals in the record. In the present studies this repetition of a definite pattern has not been observed. Grund[4] found in 2 cases that spinal anesthesia

had no effect on fasciculations. Russel, Odom and McEachern[5] noted no change in the frequency of fasciculations following peripheral nerve block. On the basis of these observations, Tower[6] concluded that the distinction between the site of origin of fibrillations and that of fasciculations is as yet uncertain.

Subsequent studies on nerve root and peripheral nerve block have yielded varying results. Swank and Price[7] noted a decrease of 50 to 65 per cent in the incidence of fasciculations following spinal anesthesia and a decrease following peripheral nerve block in 5 cases, with no alteration of frequency in 1 case. DeJong and Simons[8] observed that peripheral nerve block had no effect on the incidence of fasciculations. A possible explanation for this difference in results is afforded by the observation of Odom, Russel and McEachern[9] that peripheral nerve block had no effect on the incidence of fasciculations in 4 cases but produced a decrease in 2 others. However, in the last 2 cases fasciculations had been elicited previously only by posturing the limb, a procedure which was impossible when the muscles studied were paralyzed.

The results of spinal anesthesia and peripheral nerve block in the present investigations confirm the observations of Grund[4]; Odom, Russel and McEachern,[9] and DeJong and Simon.[8] The selection and placing of patients so as to avoid purposeful and postural movements served to prevent a false reduction in the frequency of fasciculations, as pointed out by Odom, Russel and McEachern.[9] The failure of spinal anesthesia and peripheral nerve block to decrease or abolish fasciculations indicates that the discharges giving rise to these involuntary movements cannot arise in the anterior horn cells, the nerve root or the peripheral nerve proximal to the point of block, for under such conditions blocking of the transmission of impulses should have materially altered the frequency of fasciculations. This opinion receives further support from the increase in

1. Langley, J. N., and Kato, T.: The Physiological Action of Physostigmine and Its Action on Denervated Muscle, J. Physiol. **49:** 410, 1915.

2. Pommé, B., and Noël, R.: La zone de jonction myoneurale dans quelques cas pathologiques, Rev. neurol. **2:** 1, 1934.

3. Denny-Brown, D., and Pennybacker, J. B.: Fibrillation and Fasciculation in Voluntary Muscle, Brain **61:** 311, 1938.

4. Grund, G.: Ueber die Entstehung des fibrillären Muskelzuckungen bei spinalen Amyotrophien, Deutsche Ztschr. f. Nervenh. **145:** 99, 1938.

5. Russel, C. K.; Odom, G., and McEachern, D.: Physiological and Chemical Studies of Neuromuscular Disorders, Tr. Am. Neurol. A. **64:** 120, 1938.

6. Tower, S. S.: The Reaction of Muscle to Denervation, Physiol. Rev. **10:** 1, 1939.

7. Swank, R. L., and Price, J.: Fascicular Muscle Twitchings in Amyotrophic Lateral Sclerosis: Their Origin, Arch. Neurol. & Psychiat. **49:** 22 (Jan.) 1943.

8. DeJong, H., and Simons, D. J.: A Comparative Study of Fibrillation and Tremor, J. A. M. A. **118:** 702 (Feb. 28) 1942.

9. Odom, G.; Russel, C. K., and McEachern, D.: Studies of Neuromuscular Disorders: The Myogram, Blood Cholesterinase and Effect of Prostigmine in Myasthenia Gravis and Progressive Muscular Atrophy, Brain **66:** 1, 1943.

fasciculations produced by prostigmine during spinal anesthesia or nerve block.

That the effect of curare is peripheral was first demonstrated by Claude Bernard. Kuffler [10] demonstrated that curarine decreases the sensitivity of the end plate to acetylcholine, an effect opposing depolarization and excitation. Since curare acts by blocking impulses at the myoneural junction, the abolition of fasciculations by curarization indicates that they originate at this point or proximal to it. As prostigmine fails to induce fasciculations during curarization, this may be taken as further evidence in favor of this viewpoint. During the studies on curare voluntary movement was possible, so that impulses could be conducted across the myoneural junction. It is quite possible that if fasciculations originate from discharges in the anterior horn cells or from the peripheral nerve proximal to the end plate, these impulses, likewise, could be discharged across the myoneural junction. The failure of acetylcholine and mecholyl (acetylbetamethylcholine) to influence the frequency of fasciculations is most probably due to the rapidity with which the cholinergic substances are destroyed by cholinesterases.

Denny-Brown and Pennybacker [3] pointed out that fasciculations involve neither single fibers nor whole fascicles, but are contractions of a group of fibers between these two extremes. This group of fibers, they concluded, is a motor unit. It is not possible to reconcile the contraction of all the muscle fibers innervated by a single neuron with a purely peripheral mechanism. While it is known from the work of Masland and Wigton [11] that fasciculations induced by prostigmine result in an antidromic impulse along the motor nerve, this effect cannot be considered as a possible basis for the timing of the simultaneous contraction of many individual fibers, for, among other reasons, antidromic impulses to the anterior horn cells would be blocked by spinal anesthesia and nerve block. While the timing mechanism permitting the simultaneous contraction of many fibers is not evident, the continuation of these simultaneous contractions when the muscle fibers are segregated from the central nervous system by pharmacologic block and their cessation under curarization constitute evidence, nevertheless, that their origin is peripheral, and in the region of the myoneural junction.

Although both fasciculations and fibrillations originate in the same vicinity, it is not possible, at least at present, to consider them as similar manifestations. Fibrillations occur only in completely denervated muscles, while fasciculations are seen in the absence of complete denervation.

SUMMARY

Spontaneous muscular fasciculations are not affected by spinal anesthesia or peripheral nerve block. Under these conditions the increase in fasciculations produced by prostigmine is likewise unaffected. Curare abolishes spontaneous fasciculations and prevents the induction of fasciculations by prostigmine. Fasciculations originate, therefore, not in the anterior horn cells but in the region of the myoneural junction.

111 North Forty-ninth Street.
1025 Walnut Street.

10. Kuffler, S. W.: Specific Excitability of the End-plate Region in Normal and Denervated Muscle, J. Neurophysiol. **6:** 99, 1943.

11. Masland, R. L., and Wigton, R. S.: Nerve Activity Accompanying Fasciculation Produced by Prostigmin, J. Neurophysiol. **3:**269, 1940.

TUMOR OF THE ACOUSTIC NERVE WITHIN THE PETROUS BONE

OPERATIVE REMOVAL

LEO J. ADELSTEIN, M.D, AND FRANK M. ANDERSON, M.D.

LOS ANGELES

Neoplasms arising from the sheath of the acoustic nerve are not uncommon; they comprise from 8 to 10 per cent of all intracranial tumors. Ordinarily these growths are closely applied to the portion of the nerve extending from the internal auditory meatus to the pons, and frequently there is close attachment of the tumor to the bony wall of the meatus, with erosion of that structure to a variable extent.

The case reported here is of unusual interest because the tumor arose completely within the petrous bone and did not present itself to view in the usual location. Rather, it eroded the bone extensively and was disclosed at operation

in hearing increased to a loss of at least 50 per cent and was noticeable to the patient. For this reason tonsillectomy was performed, a procedure which did not alter the course of the symptoms.

Approximately three years before admission to the hospital weakness of the right side of the face was observed. This was progressive, and within a year this side of the face became entirely paralyzed. The patient was unable to draw her mouth to the right or to raise her right eyebrow. She could partially close the eyelid by strongly closing the left eye.

There were no other subjective complaints; headache had at no time been present, and dizziness and unsteadiness in gait were never in evidence. In fact, the patient had been under observation for some time before her admission for what was thought to be Bell's palsy of the ordinary type.
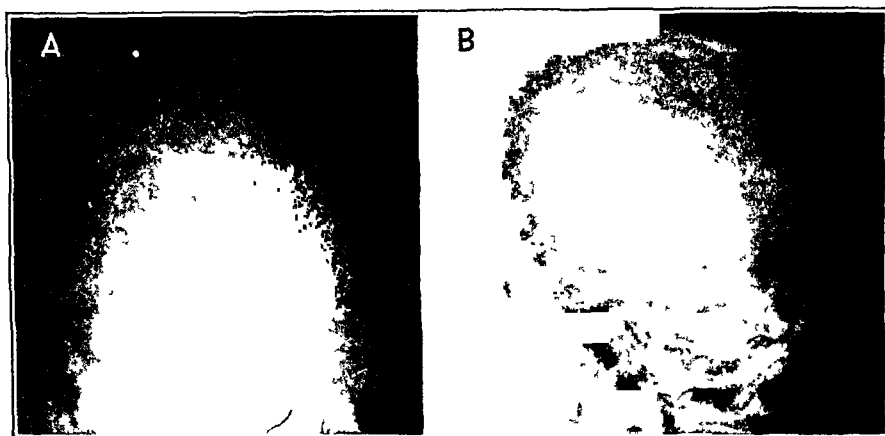
Fig. 1.—Roentgenograms of the skull, indicating (A, Towne position) extensive erosion of the ridge of the right petrous bone and (B, Stenver position) erosion in the region of the right internal acoustic meatus.

as a bulging mass on the posterior surface of the petrous pyramid, completely covered by the greatly thinned bony wall and the overlying dura.

A review of the literature did not disclose the report of such a tumor except for the microscopic growths encountered in autopsy material on serial section of the petrous pyramid.

REPORT OF A CASE

History.—A high school girl aged 15, white, six years prior to her first admission to the hospital noted the gradual onset of tinnitus and deafness in the right ear. The tinnitus never became severe, but the impairment

Examination.—On her admission to the hospital, on Jan. 3, 1940, examination showed that the patient was well developed, alert and cooperative. General physical inspection revealed no abnormalities of any sort except obvious paralysis of the right side of the face. Routine examination of the throat, ears and chest revealed nothing abnormal. Neurologic examination disclosed brief nystagmus on full left lateral gaze, slight hypesthesia over the distribution of the second division of the trigeminal nerve on the right side and total paralysis of the right side of the face, with loss of the sense of taste over the anterior two thirds of the tongue on the same side Faradic stimulation of the right facial nerve provoked no contraction of the facial muscles.

Audiometric examination disclosed perception deafness in the right ear, with loss of approximately 50 per cent in all ranges. Cold caloric stimulation of the right ear elicited no response in the horizontal semicircular canal and a delayed reaction in the vertical canals. The left labyrinth appeared normal.

Cerebellar signs were minimal; there were slight dysdiadokokinesis and asynergy in the right upper extremity, but these signs were not detected in the leg. The deep

reflexes were somewhat greater in the right extremities than in the left; there were no pathologic reflexes.

Spinal puncture revealed a pressure of 260 mm. of water, with normal dynamics and negative serologic reactions. Roentgenograms of the skull (fig. 1 *A* and *B*), taken in the Towne and Stenver positions, showed
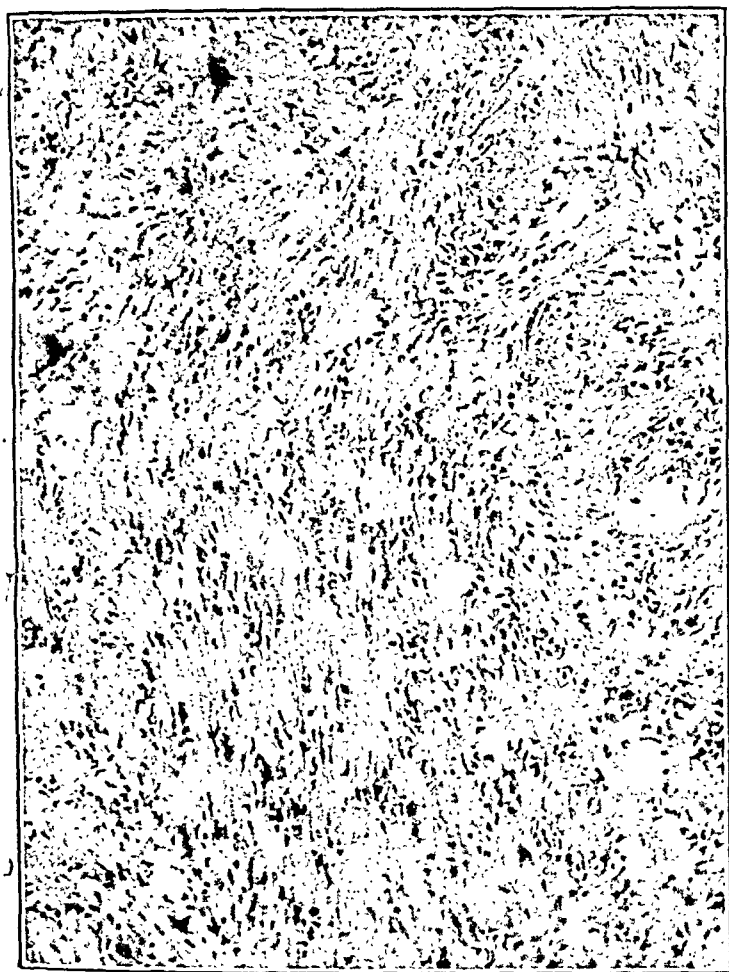
Fig. 2.—Acoustic tumor; hematoxylin and eosin stain; × 120.

erosion of the ridge of the right petrous bone in the region of the internal acoustic meatus.

Diagnosis.—The diagnostic impression before operation was that of an acoustic neuroma or a cholesteatoma in the right cerebellopontile angle.

Operation.—On January 19 a midline cerebellar incision was outlined from the inion to the third cervical spine, and the suboccipital muscles were widely retracted from the midline. The bony floor of the posterior fossa was then removed superiorly up to the torcular Herophili and inferiorly down to, and including, the posterior half of the ring of the foramen magnum. The dura over the cerebellum was tense; so the posterior horn of both the right and the left lateral ventricle was tapped, with release of the intracranial tension. The dura over the cerebellum was then opened, and the straight sinus was tied with black silk. The cisterna magna was emptied and a large amount of fluid released; this permitted a careful and easy inspection of the right cerebellopontile angle. The seventh and eighth cranial nerves on the right side were easily identified in their peripheral distribution, and no tumor was seen. With gentle retraction of the right cerebellar lobe, the base of the skull was searched carefully, and in the region of the right petrous bone a large, hard eminence was discovered, an observation which indicated at once an underlying tumor. The bony shell which presented itself was opened with a small forceps, and as large an amount of

tumor tissue as possible was removed with the aid of a small curet. A piece of the bony shell together with tumor tissue was taken for examination in order to determine their exact relation. The wound was given a thorough toilet so that at the close of the operation the operative site was entirely dry. The wound was then closed carefully in layers with black silk. The condition of the patient at the end of the operation was fair.

Postoperative Course.—The patient's convalescence was uneventful. The appearance of the face remained the same as before operation, partial closure of the right eye being possible, as it was before the operation. The deafness of the right ear was of course complete.

Pathologic Examination.—Microscopic study of the tissue removed at operation disclosed a rather dense fibrous stroma, with some tendency to bandlike arrangement and pseudopalisading of cells (fig. 2). The connective tissue had in several areas undergone a mild degree of hyalinization. One of the sections demonstrated the thin, closely approximated plate of bone which had been removed in gaining access to the tumor. The diagnosis was that of neurofibroma.

Three months later (March 25) a spinal accessory-facial nerve anastomosis was performed on the right side, the descendens hypoglossi nerve being sutured to the distal end of the accessory nerve (fig. 3).

Approximately three months after the nerve anastomosis, that is, at least two years after the paralysis of the face became complete, slight movement could be detected at the corner of the mouth on strong effort. Within the next two months considerable motion became possible, and with constant practice and physical therapy the patient has, after almost two years, attained good use of the face, with an excellent functional result.

There have been no symptoms of any nature to suggest recurrence of the tumor, and the patient is entirely free from symptoms except for deafness in the right ear.

Fig. 3.—Photograph of the patient before anastomosis of the spinal accessory and the facial nerve on the right side.

COMMENT

It is probable that the majority of acoustic neuromas arise from the portion of the nerve within the petrous bone, or in close approximation to the internal acoustic meatus. However, growth usually takes place in the direction of least resistance, i. e., medially, so that the tumor

presents itself in the posterior fossa adjacent to the pons and the cerebellar hemisphere; this makes the precise point of origin difficult of determination. Many authors have described neoplasms of the eighth nerve confined entirely to the bony canal, but such growths have without exception been small tumors, the size of a pea or less, which produced no important clinical symptoms and were discovered post mortem on section of the petrous bone. Cushing,[1] in his treatise on tumors of the acoustic nerve, cited

Fig. 4.—Photograph taken two years after operation, indicating the patient's ability to use the facial muscles

several instances of this type, as did Hardy and Crowe,[2] Fowler[3] and others.

The present case is unique in that the tumor arose within the internal auditory canal and grew to such size that it produced definite cerebellar signs, together with slight impairment of function of the trigeminal nerve, diminution of the deep

reflexes on the opposite side of the body and increase in intracranial pressure, without presenting medially through the meatus. Rather, growth took place by expansion and erosion of the bony canal itself, a feature undoubtedly made possible by the youth of the patient, who was 15 years of age at the time of operation, and this extradural bulge evidently produced sufficient compression of the cerebellar peduncles and the brain stem to create the clinical picture.

The patient had no antecedent head trauma of any sort. The theory that trauma, with perhaps a minor fissure fracture of the petrous bone, might be a factor in the origin of these tumors was tentatively advanced by Fowler.[3]

The spinal accessory–facial nerve anastomosis, although not performed until two years after paralysis of the face was complete, gave an excellent clinical result. When the face is in repose, there is practically no asymmetry, though this was very noticeable before operation, and, as a result of constant practice, the face shows remarkable ability to assume an almost symmetric smile (fig. 4). Strangely, the patient can draw back the corners of the mouth more completely by thinking of this act, as though the facial nerve were intact, than she can by elevating the shoulder (function of the accessory nerve). She has never regained the ability to wrinkle the forehead by raising the eyebrow on the affected side, although she frowns normally.

SUMMARY

In the case of a 15 year old girl who showed total paralysis of the right side of the face and high grade loss of function of the acoustic nerve associated with slight cerebellar signs on the same side, operation disclosed a neurofibroma which lay completely within the petrous pyramid and produced a bulge of this structure into the posterior fossa. The tumor was removed, and later the spinal accessory and facial nerves were anastomosed, with an excellent clinical result. Tumors of such size confined entirely to the intrapetrous portion of the acoustic nerve are exceedingly uncommon.

1930 Wilshire Boulevard.

1. Cushing, H.: Tumors of the Nervus Acusticus, Philadelphia, W. B. Saunders Company, 1917.

2. Hardy, M., and Crowe, S. J.: Early Asymptomatic Acoustic Tumors, Arch. Surg. **32**:292 (Feb.) 1936

3. Fowler, E. P.: Acoustic Tumors Within the Internal Auditory Meatus, Laryngoscope **46**:616 (Aug) 1936.

ANEURYSM OF THE VERTEBRAL ARTERY

REPORT OF A CASE IN WHICH THE ANEURYSM SIMULATED A TUMOR OF THE POSTERIOR FOSSA

H. E. YASKIN, M.D., AND BERNARD J. ALPERS, M.D.

PHILADELPHIA

Large aneurysms involving the vertebral arteries are rare. For this reason it seems desirable to record a case of a particularly large aneurysm which gave signs of a tumor of the posterior fossa, as well as to review the recorded cases with the object in mind of elucidating a group of signs which can be regarded as characteristic of the disorder.

Since Cruveilhier[1] published his case of aneurysm of the vertebral artery in 1835, 72 cases of aneurysm of the intracranial portion of the vertebral arteries have been reported. Many of the earlier papers merely cite the occurrence of the aneurysm and include few, or no, clinical and postmortem observations. ·

REPORT OF CASE

History.—W. E., a man aged 44, was admitted to the Jefferson Medical College Hospital on Oct. 14, 1942 with symptoms of four months' duration. At the onset of his illness he experienced left frontal headache, which radiated from the left suboccipital region. These attacks of pain became progressively worse and at times were associated with nausea and vomiting. Two months before admission he had taken 4 tablets (1.2 Gm.) of acetylsalicylic acid and 4 drachms (15.5 Gm.) of bromo-seltzer daily to relieve his discomfort. At that time he found that he collided with people on his left while walking on the street. When he tried to turn his head to either side, he experienced a sharp, lancinating pain in the back of his neck. He had episodes of momentary confusion and dizziness. His speech became thick, and on a few occasions he had difficulty in swallowing. He suffered from unsteadiness of gait, which became more pronounced with time. In the two weeks prior to hospitalization he believed his vision had become blurred, and he had intermittent diplopia. On the day before admission, while driving his automobile, he suffered a lapse of consciousness.

At the age of 2 years he had had an attack of poliomyelitis, with resultant atrophy of the right lower extremity. At the age of 29 he suddenly lost vision in the right eye. This condition gradually subsided, with return of vision in the affected eye. In 1934 he contracted gonorrhea. Since 1936 he had had attacks of dyspnea and precordial distress. In 1938 he had a severe injury to the head.

Examination.—The patient was poorly nourished and showed evidence of considerable recent loss in weight.

He was mentally sluggish and had difficulty in concentration and attention. There was partial loss of memory, with impairment of powers of calculation and recall. His speech was thick and slightly slurred. He walked with a reeling, ataxic gait and veered frequently to the left. He fell backward and to the left in the Romberg test. The pupils were irregular and reacted sluggishly to light. The optic disks were grayish and well defined. The retinal arteries were spastic and sclerosed, especially in the left eye. In the right eye there were evidences of old chorioretinitis. The movements of the extraocular muscles were full. On looking to the left he had rotary clockwise nystagmus. There were hypermetria and dyssynergia of both upper extremities, the greatest degree of cerebellar dysfunction being manifested in the left arm and hand. Truncal ataxia was pronounced. The deep tendon reflexes on the left were hyperactive. There were no pathologic reflexes. The abdominal reflexes were absent. Hypalgesia to pinprick was present over the anterior portion of the left side of the thorax and the left arm. A clearly defined sensory level could not be mapped out. Position sense and vibratory perception were intact. When his head was passively flexed or rotated to the right he experienced severe pain in the occipital and cervical regions. He had flaccid paresis of the right lower extremity with focal muscular wasting and areflexia, the result of his previous attack of poliomyelitis.

Percussion revealed that the heart was enlarged to the left axillary line. A presystolic mitral murmur was present. The liver was enlarged and was palpable 2 fingerbreadths below the costal margin. The blood pressure was 140 systolic and 110 diastolic.

Because of the toxic, torpid, confusional mental state and the history of excessive intake of bromo-seltzer, a diagnosis of bromide intoxication was made. The existence of a neoplasm of the left posterior fossa, involving the cerebellar hemisphere, vermis and medullary centers and pathways on that side, was likewise suspected.

Laboratory Studies.—On admission the bromide level in the blood was 90 mg. per hundred cubic centimeters. Urinalysis showed normal constituents. The blood count revealed secondary anemia. The Wassermann and Kahn reactions of the blood and the spinal fluid were negative. Lumbar puncture yielded xanthochromic fluid, under an initial pressure of 116 mm. of water; the spinal fluid contained 10 cells per cubic millimeter, and the total protein content was 116 mg. per hundred cubic centimeters. Studies of the chemical constituents of the blood gave normal values.

Roentgenograms of the chest showed enlargement of the heart to the left and a hypertensive configuration. The aorta was enlarged and tortuous. Roentgenograms of the skull and the cervical vertebrae revealed small calcified areas in the right parietal area of the skull. The pineal gland was calcified and in normal position. The electrocardiographic tracings revealed a conduction

1. Cruveilhier: Anatomie pathologique du corps humain, Paris. J. B. Baillière, 1835, vol. 2, no. 28, plate 3.

Clinical Cases of Aneurysm of Vertebral Artery Reported in the Literature

Author	Age, Yr.	Sex	First Symptoms		Other Symptoms	Signs	Spinal Fluid	Roentgenogram	Observations at Necropsy
			Nature	Duration					
Cruveilhier[1] (1835)	60	M	....	....	....	....	....	....	Aneurysm of right vertebral artery
Noll[3] (1840)	..	M	Convulsions (?)	....	....	....	....	....	Aneurysm of right vertebral artery; calcareous deposit in wall of sac
Lorne[4] (1869)	19	M	Signs of meningeal irritation	Acute onset	....	....	....	....	Ruptured aneurysm of left vertebral artery; subarachnoid hemorrhage
Echeverría[5] (1870)	67	M	Dizziness; dysphagia; inability to protrude tongue	Few months; sudden death	Weakness of limbs, with stiffness and rigidity	Inability to protrude tongue or to swallow; extreme vertigo on attempted locomotion	....	....	Ruptured aneurysm of right vertebral artery; atheroma of coats of vessels at base of brain; subarachnoid hemorrhage
Sevestre[6] (1872)	45	M	Severe headache (especially occipital) and prostration	15 days; recurrent attacks and sudden death	Paralysis of lower limbs	Flexion and paralysis of limbs; distention of bladder	....	....	Ruptured aneurysm of left vertebral artery; slight atheromatous changes in coats; second pea-sized, unruptured aneurysm of left vertebral artery; subarachnoid hemorrhage
Schultze[7] (1875)	56	M	Convulsive tic of muscles of left side of face except frontalis	12 months	....	Progressive paresis of muscles of left side of face except frontalis	....	....	Unruptured, "cherry stone-sized" aneurysm of left vertebral artery in intimate association with 7th and 8th cranial nerves on left
Osler[8] (1880)	36	M	Sudden collapse and death	....	....	....	....	....	Ruptured small aneurysm of left vertebral artery; subarachnoid hemorrhage; sclerotic walls; endarteritis
Möser[11] (1884)	61	M	Progressive bulbar palsy	12 months	....	Signs of progressive bulbar palsy; four days before death bruit on each side between mastoid and vertebral column	....	....	Fusiform aneurysm of left vertebral artery, measuring 20 by 12 mm.; medulla compressed and distorted; fatty degeneration of intima
Ladame and von Monakow[14] (1900)	..	..	....	....	....	General motor incoordination; complete analgesia of right side of body; diplopia; irregular pulse	....	....	Saccular aneurysm of right vertebral artery, size of pigeon's egg; compression of left side of pons, cerebellum and medulla; vessels atheromatous
Hedinger[15] (1905)	50	M	Violent headache, with vomiting and disturbance of consciousness	14 days before death	....	Left hemiplegia of 8 years' duration	....	....	Unruptured aneurysm of right vertebral artery; localized syphilitic periarteritis of aneurysm
Rindfleisch[16] (1905)	51	F	Severe suboccipital headache and feeling of anxiety	6 days, followed by deep stupor	Headache for 3 yr.	Deep stupor; fundi showed hemorrhages and edematous disks; sudden deep coma; slow pulse	Initial pressure 32 mg. Hg; bloody fluid	....	Ruptured aneurysm, size of bean, in right vertebral artery; subarachnoid hemorrhage
Beadles[17] (1907)	65	F	Gradual development of palsy of right side of face and right hemiplegia, with progressive bulbar palsy	1 year	Psychosis of organic type, with cerebral arteriosclerosis	Paralysis of right side of face and right limbs; bulbar palsy; partial deafness	....	....	Unruptured, calcified aneurysm, size of pea, in left vertebral artery; pressure against roots of nerves in cerebellopontine angle; atrophy of tissue on left side of medulla; recent hemorrhage in left cerebral hemisphere; arteriosclerosis
Ruston and Southard[18] (1906)	60	F	Sudden, boring suboccipital pain, with projectile vomiting	10 days	Drowsiness for 1 yr., dull ache in suboccipital region between acute episodes; sudden death from respiratory failure	Slow pulse	....	....	Fusiform aneurysmal dilatation of both vertebral arteries; miliary cerebral aneurysms with rupture
Longcope (1909)	57	M	Headache	6 years	More severe headache before admission; episode of unconsciousness	Retraction of head; paralysis of right lower extremity; delirium; episode of unconsciousness	Bloody	....	Ruptured aneurysm of vertebral artery, with subarachnoid hemorrhage
Wichern[20] (1911)	42	M	Headache and stiffness of neck; sudden coma before admission	2 months	Coma with stiffness of neck on admission	Stiffness of neck	Bloody	....	Ruptured aneurysm of left vertebral artery, size of pen; thickening of vessels

Reference	Age	Sex	First symptoms	Duration	Course of disease	Physical findings	Spinal fluid	Other findings	Anatomic diagnosis
Bailey [21] (1913)	37	M	Stiffness of neck; weakness of right arm	2-3 years		On admission, severe shooting pains in back of neck, radiating to head, and paresthesias of right extremities	....	....	Aneurysm of right vertebral artery, compressing high cervical part of cord; endarteritis
Weidman [10] (1915)	40	M	Chills and sweats, followed by unconsciousness	1 hour		On admission, flaccid quadriplegia; sensory level to 2d cervical dermatome	Bloody	....	Ruptured aneurysm of right vertebral artery; proliferative endarteritis
Hedinger [22] (1917)	47	F	Recurrent pain in back of neck and shoulders after fall	4 years		Signs of meningeal irritation and attacks of opisthotonos; papilledema in left eye with hemorrhages in fundus	....	....	Ruptured aneurysm of left vertebral artery; subarachnoid hemorrhage
Kerppola [23] (1919)	28	M	Headache; pressure in head and attacks of vertigo	Weeks	Recovery of consciousness, followed by irrationality and somnolence; convulsions and death five days later		....	....	Ruptured aneurysm of right vertebral artery
Wells [25] (1922)	54	M	Episodic headaches	8 to 10 years	Syncopal attacks for 3 yr.; pain in face and teeth for 2 yr.; ataxia, weakness, incontinence, progressive bulbar palsy, vertigo and roaring in ears 1-2 mo.	No paralysis noted	....	....	Unruptured saccular aneurysm of left vertebral artery (35 by 34 by 30 mm.), with compression of pons, cerebellum, medulla and roots of 6th to 9th cranial nerve
Packard and Zabriskie [20] (1925)	50	M	Sudden occipital headache; pain in back and legs and drooping of left eyelid	2 weeks	Sudden death of apoplexy 2 wk. after onset of symptoms	Paralysis of left 3d, 4th and 6th cranial nerves, with fixed left pupil	Yellowish fluid, under moderate pressure; 50 cells per cu. mm.; Wassermann reaction negative; no increase in globulin	....	Ruptured aneurysm of left vertebral artery, with subpial hemorrhage
Conway [27] (1926)	40	F	Pain in left side of face; subjective vertigo and unsteady gait, associated with episodic attacks of pain	2 years		Palsy of right side of face, paresis of left limbs; weakness of both external rectus muscles; bilateral optic neuritis	Abundant red blood cells in fluid	....	Unruptured aneurysmal tumor of left vertebral artery, with invasion of cerebellum; atheromas present
Keegan and Bennett [29] (1931)	50	F	Intense pain in suboccipital region and neck, followed by convulsions and coma; recovery	8 years	Ataxia and weakness 7 yr. after onset, with medullary paralysis 1 yr. later	Signs of meningeal irritation at initial attack; ataxia and nystagmus 7 yr. later	Bloody spinal fluid at initial attack; clear fluid 7 yr. later; serologic reactions negative	....	Unruptured, oval aneurysm, 2.5 cm. in diameter, of left vertebral artery
	56	M	Coma and death	4-6 hours			Bloody fluid; serologic reaction negative	....	Ruptured aneurysm of right vertebral artery, 5-10 mm. in diameter, with basilar subarachnoid hemorrhage
Currier and Davis [9] (1933)	45	F	Sudden onset of severe headache and pain in neck	2 months	Attacks of unconsciousness, with recovery; personality change after first coma; sudden death	Negative results of neurologic examination	Bloody fluid after first coma, becoming xanthochromic; serologic reactions negative	....	Ruptured aneurysm of right vertebral artery, 9 by 4 mm., with subarachnoid hemorrhage
Dial and Maurer [29] (1937)	2	M	Trauma to head, with fracture of skull and unconsciousness; sudden coma 5 days after recovery	Coma 5 days after return of consciousness		Signs of meningeal irritation and medullary collapse	Bloody fluid	Fracture of left frontal bone	Ruptured aneurysm of right vertebral artery
Maass [30] (1937)	35	M	Severe headache	1 day before death	Unconsciousness	Positive Babinski sign	Bloody fluid; positive Wassermann reaction	....	Small ruptured aneurysm at junction of both vertebral arteries with basilar artery; syphilis
	?	F	Coma and death	....			Bloody	....	Small ruptured aneurysm of right vertebral artery; syphilis
Dandy [34] (1937)	63	F	Progressive deafness and tinnitus in left ear	1 year	Year after onset, attacks of dizziness with nausea and vomiting with any quick movement; in sequence, unsteadiness of gait and progressive deafness	Unsteadiness of gait; diminution of left corneal reflex	....	....	Operation revealed aneurysm under left 8th cranial nerve; aneurysm continuous with left vertebral artery

Clinical Cases of Aneurysm of Vertebral Artery Reported in the Literature—Continued

Author	Age, Yr.	Sex	First Symptoms		Other Symptoms	Signs	Spinal Fluid	Roentgenogram	Observations at Necropsy
			Nature	Duration					
Boyd and Werblow[21] (1937)	57	F	Sudden excruciating pain in right lumbar region (dissecting aortic aneurysm); choking sensation in neck, with nausea and vomiting	1 week	Initial symptoms merged into stupor; paralysis of left extremities and left side of face; convulsion and death	Signs of stupor; blood pressure 200/75; arteries of fundi sclerotic	....	....	Unruptured fusiform aneurysmal dilatation of terminal portion of left vertebral artery; compression of left cerebellar hemisphere by aneurysm; atherosclerosis; dissecting aortic aneurysm, with coarctation of aorta
Loder[22] (1938)	67	M	Paroxysms of sharp pain behind right ear, radiating down neck, especially when head was turned to left	1 year	15 yr. before last illness, vertiginous, syncopal attack with residual weakness of left side of face and left hand, which cleared; with last attack, diminished hearing in right ear, ataxia and progressive bulbar palsy	Palsy of left side of face, ataxia; generalized cerebellar dysfunction, especially on right; progressive signs of bulbar palsy toward end of clinical course	.....	....	Unruptured vertebral ovoid aneurysmal mass of right artery, compressing adjacent portion of medulla, cerebellar hemisphere and cranial nerves, 7th to 12th inclusive, on same side
Bassoe[33] (1939)	31	F	Headache; pain over vertex, occiput and back of neck	~6 months	1914: delirium; 1916: cramps in legs, dizziness; 1937: weakness in left side of body; pain about left ear, radiating down to left side of body	1914: stiff neck; 1916: hypalgesia on right side of body; 1937: left hemiparesis	1914: fluid bloody and under increased pressure; 1916: fluid clear; 1937: fluid clear; 7 cells per cu. mm.; Wassermann reaction negative; total protein 99.0 mg. per 100 cc.	....	Saccular aneurysm of left vertebral artery, compressing adjacent portions of pons and medulla; syphilitic arteritis; multiple smaller aneurysms of basilar artery; syphilitic aortitis
	63	M	Dizziness and severe headache	5 years	2 yr. after onset, numbness of left side of body, paresis of left leg; 5 yr. after onset, severe vertiginous spells and convulsions	Bilateral pyramidal tract signs; hypalgesia on left side of body; thick speech; ataxia of right hand	Fluid clear: 7 cells per cu. mm.; Wassermann reaction negative	....	Operation revealed "vascular aneurysm with tremendous enlargement of left vertebral artery"
Richardson and Hyland[35] (1941)	49	M	Tinnitus in left ear and occipital headache	2 years	Psychosis for 10 yr.; deafness of left ear; numbness of left side of face; diplopia; ataxia	Left hemiparesis; nystagmus on left lateral gaze; palsies of left 3d, 5th, 6th, 7th and 8th cranial nerves	....	Ventriculogram showed marked dilatation of ventricular system	Dumbbell-shaped, nodular aneurysm, 5 by ? by 2 cm, compressed against anterolateral aspect of left side of pons and filling cerebellopontile angle; attached to trunk of right vertebral artery
Globus and Schwab[36] (1942)	50	F	Severe drawing pains in left side of neck and episodic dizziness	6 years	Periodic headaches; difficulty with speech and deglutition; generalized weakness; insomnia	Slight left hemiparesis; broad-based gait; bilateral papilledema and postneuritic optic atrophy; horizontal nystagmus bilaterally; palatal paralysis	Clear; 3 cells per cu. mm.; initial pressure 108 mm. of water; total protein 61 mg. per 100 cc.; Ayala index 5.5	Roentgenogram negative; ventriculogram: marked dilatation of lateral ventricles, with right slightly larger than left	Unruptured aneurysm (1.5 by 1 by 0.75 inch) of left vertebral artery, compressing inferior surface of cerebellum and left side of medulla and pons; extension into foramen magnum; proliferative endarteritis
Yaskin and Alpers (1943)	44	M	Left suboccipital pain and left frontal headache	4 months	Vertigo for 3 yr. Last 4 mo.: bromidism; ataxic gait, with veering to left. Vertiginous attacks; change in position of neck caused severe nuchal pain; thick speech; occasional dysphagia	Mental torpidity; left rotary nystagmus; bilateral cerebellar dysfunction of limb and trunk, more marked on left; pyramidal tract signs on left; hypalgesia to 2d dorsal level on left	Xanthochromia; initial pressure 160 mm. of water; total protein 116 mg. per 100 cc.; serologic reaction negative	....	Large, unruptured saccular aneurysm of left vertebral artery, with regional compression of medulla, cerebellum and upper cervical part of cord; generalized atherosclerosis

deformity of the entire ventricular complex, which indicated a severe grade of myocardial impairment. There was pronounced left axis deviation. The visual fields were normal.

Audiometric tests showed a 29 per cent loss of hearing for speech in the left ear and an 18 per cent loss in the right ear. In the caloric tests the most striking observation was the absence of past pointing on stimulation of all canals on the left side, an indication of the possible presence of a lesion in the cerebellar nuclei of the same side.

The electroencephalographic tracings showed poorly developed abnormal waves over the right frontal lobe.

Course of Illness.—The bromidism was treated with large doses of sodium chloride, hydration and intramuscular injections of desoxycorticosterone acetate (2.5 mg. twice a day). After one month the bromide
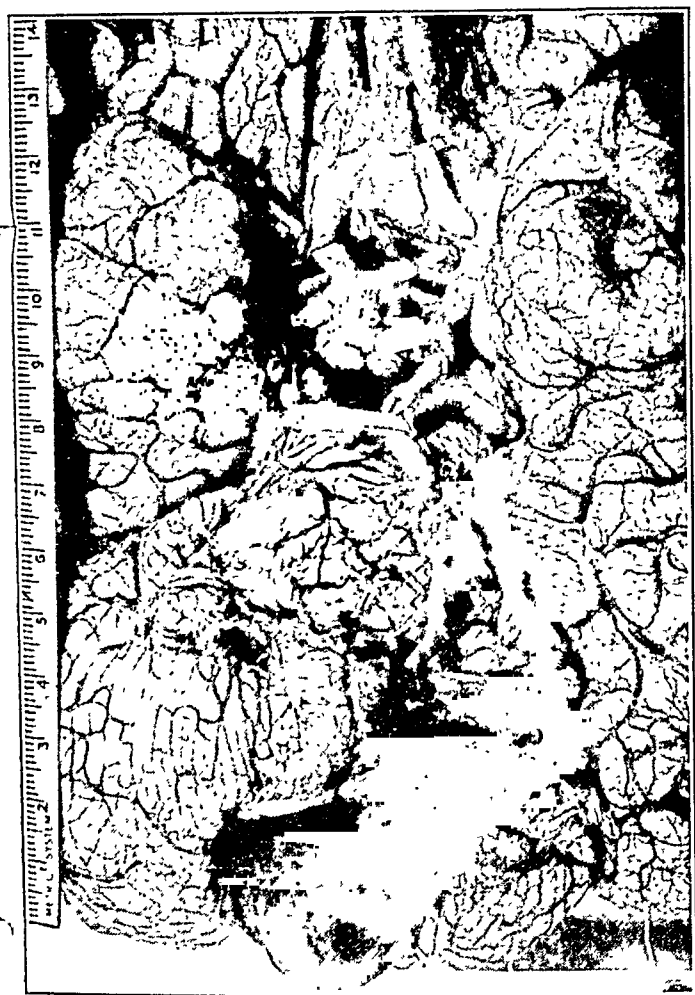
Large saccular aneurysm of the left vertebral artery, with regional compression of the medulla and cerebellum.

content of the blood was too low to read. The neurologic picture was still characterized by nystagmus, cerebellar dysfunction, especially in the left extremities, and suboccipital pain on rotation of the neck. In addition, paresis had developed in the left limbs, particularly in the arm, with hyperreflexia in these members. A sensory level for pinprick was present at the second cervical dermatome on the left side. Because of the pain in the neck and the sensory level, a tumor in the high cervical portion of the cord, projecting into the posterior fossa, was suspected. Lumbar puncture, performed on November 12, revealed yellow-tinged fluid, under an initial pressure of 200 mm. of water. The total protein of the spinal fluid measured 69 mg., the sugar 67 mg. and the chlorides 709 mg. per hundred cubic centimeters.

The patient's poor physical condition, together with the development of a severe infection of the urinary

tract, delayed the consideration of an exploration of the posterior fossa. On November 24 symptoms of respiratory collapse developed, and he died.

Necropsy.—The scalp, skull and meninges were normal. The brain weighed 1,500 Gm. The cerebral hemispheres were symmetric in size and shape. Inspection of the base of the brain revealed that the left vertebral artery was tremendously dilated and coiled on itself to form a saccular tumor mass with a smooth surface (figure). The aneurysm measured 6.5 cm. in length, 3 cm. in depth and 2 cm. in diameter. It had not ruptured, and the entire lumen contained an antemortem thrombus. An excavation extending into the adjacent basilar portion of the left cerebellar hemisphere and the left side of the vermis had been made by the aneurysm, and the medulla was compressed and displaced to the right. The upper cervical portion of the cord was compressed to a lesser degree. The right vertebral artery was hypoplastic and measured about 1 mm. in diameter. The remaining vessels of the circle of Willis showed arteriosclerotic thickening and formation of plaques. There were no other aneurysms of the intracranial arteries.

Diagnosis. — The anatomic diagnoses were saccular aneurysm of the left vertebral artery, with a massive antemortem thrombus; regional compression of the medulla, cerebellum and high cervical portion of the cord; pronounced generalized atherosclerosis; cirrhosis of the liver; acute necrotizing cystitis; penetrating abscess of the fundus of the urinary bladder, and calculus of the pelvis of the right kidney.

The cause of death was aneurysm of the left vertebral artery with medullary compression.

SURVEY OF LITERATURE

Allusion has already been made to the rarity of aneurysm of the vertebral arteries. This is emphasized by the statistics of McDonald and Korb,[2] who, from 407 articles published before Jan. 1, 1938, compiled 1,125 cases of saccular aneurysm of the arteries at the base of the brain, verified by necropsy or operation. They found that in a series of 1,023 cases of aneurysm the location of which had been verified, only 59 were reported in which the vertebral arteries were involved. We were able to find 8 more verified cases of aneurysm of the vertebral arteries recorded since 1938, including the case here reported, the total number of verified cases now being 67.

Cruveilhier,[1] in 1835, reported on an aneurysm which involved the right vertebral artery. It occurred in a man aged 60 who had several aortic aneurysms. The pons was deeply depressed. Neill[3] reported a case of ruptured aneurysm of the right vertebral artery in "a man who suffered with affection of the nervous system, I think epilepsy." The walls of the sac were thickened by calcareous deposits in the middle coat of the artery. Lorne[4] observed a ruptured aneurysm of the left vertebral artery in a boy who had died after an acute

2. McDonald, C. A., and Korb, M.: Intracranial Aneurysms, Arch. Neurol. & Psychiat. **42:** 298 (Aug.) 1939.

3. Neill, J.: Contribution to Pathological Anatomy, Am. J. M. Sc. **18:**122 (July) 1849.

4. Lorne: Anévrysma de l'artère vertébrale, Bull. Soc. anat. de Paris **44:**455 (Nov.) 1869.

meningeal syndrome. Echeverria[5] described the case of an elderly man who had suffered from attacks of dizziness, inability to protrude the tongue, dysphagia and difficulty in locomotion for months before his death. Examination revealed dysarthria and partial paralysis of the limbs, which were stiff and rigid. The patient died suddenly while straining at stool. Necropsy revealed a ruptured aneurysm of the right vertebral artery. The vertebral arteries and those at the base of the brain were in a state of fatty and atheromatous degeneration. The ninth, tenth, eleventh and twelfth cranial nerves on the right side were compressed by the aneurysmal sac, a condition explaining the paralysis of the tongue and the dysphagia. Sevestre[6] reported a case of a man of middle age who had recurrent attacks of prostration associated with severe headache, especially in the occipital region. In one of these attacks both lower extremities were paralyzed. At necropsy subarachnoid basilar hemorrhage was prominent. In the left vertebral artery were two small aneurysms approximately 0.5 cm. in diameter. Only one of these was ruptured.

Many of the cases reported concern small aneurysms, such as that of the left vertebral artery, recorded by Schultze,[7] which was the size of a cherry stone and was unusual in producing a prominent convulsive tic involving the musculature of the left side of the face. In this case death resulted from a pulmonary disorder. Necropsy showed an aneurysm near the opening of the porus acusticus internus and in intimate relationship with the facial and auditory nerves. A number of the small aneurysms of the vertebral artery were discovered at necropsy after sudden death from subarachnoid hemorrhage. Osler[8] reported such a case, in which a ruptured aneurysm was observed in a young man who had previously been free of cerebral symptoms. Currier and Davis[9] and Weidman[10] likewise reported cases of a ruptured vertebral aneurysm. In their cases pain in the neck was prominent shortly before death. Möser[11] recorded a case of aneurysm of the left vertebral artery which occurred in a man aged 61, who suffered from mitral endocarditis. Symptoms of a progressive bulbar lesion had existed for a long time. Four days before death a loud murmur was heard on each side between the mastoid region and the vertebral column. At necropsy the aneurysm, which was fusiform and measured 20 by 12 mm., was observed to compress the anterior surface of the medulla. With this case, Möser reported 2 cases in which an aneurysm of the vertebral artery, noted post mortem, had not produced symptoms.

Eppinger[12] also reported a case of aneurysm of the right vertebral artery in a woman aged 30. The aneurysm was 6 mm. in diameter and had caused no known neurologic symptoms. In 1894 von Hofmann[13] published an analysis of 78 cases of intracranial aneurysm, in 10 of which the lesion occurred in the vertebral artery. In all 10 of these cases the aneurysm had ruptured and caused sudden death but had not been observed clinically. Ladame and von Monakow[14] observed an aneurysmal dilatation of the left vertebral artery, "the size of a pigeon's egg," which had produced degeneration of the pons, cerebellum, olive, pyramid and left auditory nerve. The fifth, sixth, ninth and tenth cranial nerves on the left side were slightly atrophic. The patient had had symptoms of cerebellar dysfunction for two years before death. The aneurysm in Hedinger's[15] case occurred in the right vertebral artery and was the size of a hazelnut. The patient had had syphilis for twenty-three years and for the last eight years had presented left hemiplegia. Fourteen days before death violent headache occurred, with associated vomiting, slowing of the pulse and disturbance of consciousness. Rindfleisch[16] recorded the case of a woman aged 51 who had had headache for three years. Six days before death she experienced sudden suboccipital pain and extreme anxiety. She became comatose in three days. Necropsy revealed subarachnoid hemorrhage and a ruptured aneurysm of the right vertebral artery, "the size of a bean." Beadles,[17] in his compilation of 555 cases of intracranial aneurysm, reported only 1 case in which the vertebral artery was involved. He personally observed an aneurysm, the size of a pea, at the junction of the vertebral and the inferior cerebellar artery on the left side, which compressed the medulla and the roots of the seventh, eighth, ninth and twelfth cranial nerves on that side. The patient, an elderly woman, had been admitted to an institution because of dementia of organic origin two and one-half years before her death. She had paralysis of the left side of the face, deafness, weakness of the right arm, which gradually increased, and signs of bulbar palsy. She died a few days after a sudden apoplectic stroke. A large, recent hemorrhage was present in the left cerebral hemisphere. Ruston and Southard[18] reported a case of miliary cerebral and gross bilateral vertebral aneurysms, in which they emphasized suboccipital pain as an important clinical feature. The patient, a woman aged 69, had had episodes of drowsiness for a year. About two weeks prior to her death she experienced an attack

5. Echeverria, M. G.: On Epilepsy, New York, W. Wood & Co., 1870, p. 124.

6. Sevestre: Anévrysme de l'artère vertébrale gauche, Bull. Soc. anat. de Paris 47:415 (Oct.) 1872.

7. Schultze, F.: Linksseitiger Facialiskrampf in Folge eines Aneurysma der Arteria vertebralis sinistra, Virchows Arch. f. path. Anat. 65:385 (Dec.) 1875.

8. Osler, W.: Endarteritis and Aneurysmal Dilatation of the Left Vertebral and First Part of the Basilar Arteries, Montreal Gen. Hosp. Rep. 2:16, 1880.

9. Currier, F. P., and Davis, D. B.: Intracranial Aneurysms, J. Michigan M. Soc. 35:25 (Jan.) 1936.

10. Weidman, F. D.: Ruptured Aneurysm of the Right Vertebral Artery, J. A. M. A. 65:1105 (Sept. 25) 1915.

11. Möser, H.: Beitrag zur Diagnostik der Lage und Beschaffenheit von Krankheitsherden der Medulla oblongata, Deutsches Arch. f. klin. Med. 35:418 (Sept.) 1884.

12. Eppinger, H.: Pathogenesis der Aneurysmen, Arch. f. klin. Chir. 35:1, 1887.

13. von Hofmann, E.: Ueber Aneurysmen der Basilarterien und deren Ruptur als Ursache des plötzlichen Todes, Wien. klin. Wchnschr. 7:823 (Nov.) 1894.

14. Ladame, P., and von Monakow, C.: Anévrysme de l'artère vertébrale gauche, Nouv. iconog. de la Salpêtrière 13:1, 1900.

15. Hedinger, E.: Aneurysma der Arteria vertebralis dextra, Cor.-Bl. f. schweiz. Aerzte 35:261 (April) 1905.

16. Rindfleisch, W.: Zur Kenntnis der Aneurysmen der basalen Hirnarterien und der bei den intrameningealen Apoplexien auftretenden Veränderungen der Cerebrospinalflüssigkeit, Deutsches Arch. f. klin. Med. 86:183 (Dec.) 1905-1906.

17. Beadles, C. F.: Aneurisms of the Larger Cerebral Arteries, Brain 30:285 (Oct.) 1907.

18. Ruston, W. D., and Southard, E. E.: Cerebral Seizures with Suboccipital Pain: Miliary Cerebral and Gross Vertebral Aneurysms, Boston M. & S. J. 154:312 (March) 1906.

of sudden, severe, boring pain in the suboccipital region, associated with projectile vomiting. She died suddenly. At necropsy both vertebral arteries were observed to contain fusiform aneurysmal dilatation, 0.75 cm. in diameter, which had not ruptured. Boinet's [19] specimen involved the left vertebral artery, 5 mm. below the basilar artery. The walls of the aneurysmal sac were thickened and hard. Many gummas were present on the surface and in the substance of the brain. There was no clinical history because the patient had been admitted to the hospital in coma. The case reported by Wichern [20] was that of a man who, two months prior to his admission to a hospital, had a stiff neck and headache. He was known to have had syphilis for twenty-four years. He was admitted in coma, with stiffness of the neck and no pupillary reactions. In two days he had return of consciousness. He complained of stiffness of the neck and headache. Lumbar puncture yielded bloody fluid on repeated occasions. About three weeks after admission he had a generalized convulsion and died. Necropsy revealed a ruptured aneurysm, the size of a pea, in the left vertebral artery. In Bailey's case,[21] that of aneurysm of the right vertebral artery, there was a history of weakness of the right arm and stiffness of the neck for two or three years. Four months before the patient's death he began to experience severe, sharp, shooting pains in the back of the neck, which radiated to the top of his head. The paresis of the right upper extremity progressed, and tingling and numbness were felt in the right hand and foot. He became bedfast as a result of flaccid paralysis of all the extremities. The knee jerks were hyperactive. Anesthesia of the body was present up to a line corresponding to the distribution of the second cervical segment. Death resulted from pulmonary edema. At necropsy an extensive aneurysm of the right vertebral artery was discovered. This compressed the spinal cord in its highest portion. The affected artery was the seat of advanced endarteritis.

In Hedinger's [22] case a woman aged 47 had suffered from typical migraine for many years. In 1913 she fell down a series of steps and struck her neck and the back of her shoulders. For one week thereafter she had severe pain in the back of the neck. After the accident she had frequent episodes of pain in the shoulders and neck. Four years later she had sudden, severe pain in the back of her neck, and on the following day she was found dead. Necropsy disclosed an aneurysm of the left vertebral artery, which was 1 cm. long and 0.5 cm. wide, and hemorrhage over the base of the brain.

Cases have been reported with no clinical signs or with scant clinical data. Thus, Kerppola [23] reported

that his patient complained of headache, pressure in the head and attacks of vertigo during the last few weeks of life. No clinical signs were mentioned. At necropsy an aneurysm of the right vertebral artery was observed. Morrow [24] described a spontaneously healed fusiform aneurysm of the right vertebral artery, discovered in a body used for dissection in a medical school. No history was available. The medulla was pressed into an unrecognizable mass by the large aneurysm. The walls of the vessels of the circle of Willis showed no table sclerosis. A case with a history of trauma to the head was cited by Wells.[25] At the age of 18 years his patient had a severe injury to the head, followed by unconsciousness, which persisted for three or four days. He began to complain of severe headache when he was about 40 years old and had repeated syncopal attacks three years before his death, at the age of 54. In progression, there developed roaring in his ears, diplopia, pain in the left side of his face and the teeth on that side, unsteadiness and weakness of gait and paresis of his lower limbs. He lost control of the bowel and bladder and displayed a bulbar syndrome, with inability to swallow or articulate properly. Death was due to pneumonia. Necropsy revealed a large, ovoid, unruptured saccular aneurysm of the left vertebral artery, which compressed the adjacent portions of the pons, cerebellum and medulla, as well as the roots of the sixth to the ninth cranial nerve on the same side.

An interesting case was described by Packard and Zabriskie.[26] Two weeks before his death, from apoplexy, a man aged 50 suddenly had fronto-occipital headache and pain in the back and legs and was unable to open the left eye. Examination revealed complete ophthalmoplegia on the left side. The left pupil was fixed; the right pupil responded in accommodation but not to stimulation with light. Studies of the blood and spinal fluid revealed nothing abnormal. The patient died suddenly. Necropsy showed a ruptured aneurysm, measuring 5 cm. in length and 0.75 cm. in diameter. in the left vertebral artery. The authors expressed the belief that leakage from the sac must have occurred at the onset of symptoms. The blood had burrowed forward and had collected in a mass, involving the third, fourth and sixth cranial nerves on the left side.

Conway's [27] case, again, emphasizes the prevalence of occipital or nuchal pain as a prominent symptom. His patient, a woman aged 40 years, two years before admission to the hospital experienced paroxysms of pain over the left side of the lower jaw and the lower left side of the face, the attacks often being associated with dizziness and disturbance of gait. Shortly before her admission to the hospital she had severe pain in the back of the neck. She soon became stuporous. Examination revealed palsy of the right side of the face and paresis of the left extremities, palsy of both external rectus muscles and optic neuritis. She died suddenly. Necropsy revealed evidence of old hemorrhage over the cerebellum and an unruptured aneurysmal dilatation of the left vertebral artery, which had compressed the cerebellum. Atheromas were present to a notable degree in the cerebral vessels.

19. Boinet, E.: Anévrisme syphilitique de l'artère vertébrale gauche, Compt. rend. Soc. de biol. **69**:210, 1910.

20. Wichern, H.: Zur Diagnose perforierender Aneurysmen der Hirnarterien, München. med Wchnschr. **58**:2724 (Dec.) 1911; Deutsche Ztschr. f. Nervenh. **44**:220 (May) 1912.

21. Bailey, P.: Aneurysm of the Vertebral Artery, M. Rec. **83**:266 (Feb.) 1913.

22. Hedinger, E.: Die Bedeutung des indirekten Traumas für die Entstehung der Aneurysmen der basalen Hirnarteries, Cor.-Bl. f. schweiz. Aerzte **47**:1393 (Oct.) 1917.

23. Kerppola, W.: Zur Kenntnis der Aneurysmen an den Basalarterien des Gehirns mit besonderer Berücksichtigung der begleitenden Arteriosklerose in denselben Gefässen, Arb. a. d. path. Inst. d. Univ. Helsingfors **2**:115 (Aug.) 1919.

24. Morrow, J. F.: Aneurysm of Vertebral Arteries, M. Rec. **100**:894 (Nov.) 1921.

25. Wells, H. G.: Intracranial Aneurysm of the Vertebral Artery, Arch. Neurol. & Psychiat. **7**:311 (March) 1922.

26. Packard, M., and Zabriskie, E. G.: Basal Cerebral Hemorages, J.A.M.A. **85**:1633 (Nov. 21) 1925.

27. Conway, J. A.: Two Cases of Cerebral Aneurysm Causing Ocular Symptoms, with Notes of Other Cases, Brit. J. Ophth. **10**: 78 (Feb.) 1926.

The association of convulsions with vertebral aneurysm is illustrated by the case reported by Keegan and Bennett.[28] The condition was of eight years' duration and was characterized by the sudden onset of intense pain in the back of the head, followed quickly by generalized convulsions and unconsciousness, which lasted for several hours. The patient showed signs of meningeal irritation and slight weakness of the right side of the face. Lumbar puncture yielded bloody fluid, under an initial pressure of 14 mm. of mercury. In three weeks the attacks recurred. About seven years later she had weakness in gait, nystagmus and ataxia. Studies of the blood and spinal fluid revealed nothing abnormal. Blood pressure was 210 systolic and 125 diastolic. Over a period of a year her weakness progressed, and she suddenly manifested signs of progressive failure of the medullary centers and died. Necropsy revealed an unruptured, oval aneurysm of the left vertebral artery, 2.5 cm. in diameter, which had notably compressed the adjacent portion of the medulla. There was no subarachnoid hemorrhage. It is obvious that eight years before she had experienced a rupture of this aneurysm, which had healed. The authors included another case of aneurysm, of the vertebral artery in this instance, which had ruptured and produced a massive basilar subarachnoid hemorrhage. The patient had been comatose on admission, and there was no antecedent clinical history.

The etiologic role of trauma in the production of vertebral aneurysm is illustrated by the case of Dial and Maurer.[29] In a number of cases already cited trauma seems to have precipitated acute symptoms of an aneurysm already established, but Dial and Maurer reported the case of a 2 year old child who sustained a fracture of the skull, with unconsciousness, and who, five days after apparent recovery, suddenly became comatose, with rigidity of the neck and signs of failure of medullary function. Death occurred twenty-nine days after the onset of symptoms. Necropsy revealed a small ruptured aneurysm of the right vertebral artery. The authors could not conclude whether the lesion was traumatic or congenital in origin.

Although syphilis is not regarded as a common cause of intracranial aneurysm, it can apparently produce such a lesion. Thus, Maass,[30] in a review of aneurysms of the brain due to syphilis, reported a case of a small aneurysm of this origin at the junction of the vertebral arteries and the basilar artery. He also cited a case of sudden rupture of a small syphilitic aneurysm of the right vertebral artery, without clinical details.

Boyd and Werblow[31] recorded an interesting case of coarctation of the aorta, dissecting aneurysm of the aorta and aneurysm of the left vertebral artery. They noted that since the circulation for the lower half of the body is derived almost entirely from the subclavian arteries in cases of aortic coarctation, it is not surprising that the vertebral artery, representing the first branch of the subclavian artery and participating in the formation of a collateral circulation, should become enlarged and dilated. In the authors' case the aneurysmal dilatation caused partial pressure atrophy of the left cerebellar hemisphere.

Loder's[32] case is a good example of the type of medullocerebellar syndrome which is frequently produced by the chronic, large, unruptured type of aneurysm of the vertebral artery. A man aged 67, fifteen years before admission to the hospital, had a vertiginous, syncopal attack while driving his car. He had minimal palsy of the left side of the face and paresis of the left hand, which cleared in three weeks. One year before his entrance to the hospital he noted paroxysms of sharp, shooting, stabbing pain behind the right ear, which radiated down the neck and was usually precipitated by his bending over and suddenly turning his head, especially to the left. The pain in time became constant. Diminution of hearing, more pronounced on the right, soon developed. He experienced momentary severe vertigo, followed by episodes of unconsciousness. The gait became unsteady, and he tended to stagger to the right. The headaches became more pronounced, the pain radiating to the right temporal and frontal regions, and he began to have difficulty in swallowing solid foods. Examination revealed palsy of the left side of the face, a diminished gag reflex on each side, profound generalized weakness and ataxic gait, with dyssynergia and dysmetria in all limbs, especially those on the right side. In the hospital progressive bulbar palsy developed, with inability to swallow solids and liquids. He died of pneumonia. Necropsy revealed a distinct, ovoid tumor, measuring 2.5 by 2 by 3 cm., emerging from the right vertebral artery. The aneurysmal mass produced a hollow excavation in the adjacent portion of the medulla, which was displaced to the left. The mass also compressed the adjacent basilar portion of the right cerebellar hemisphere. The seventh to the twelfth cranial nerve on the same side showed evidence of compression.

Bassoe[33] reported a case of aneurysm of syphilitic origin. A woman aged 31, known to be infected with syphilis, began to have headaches six months before her admission to the hospital. Immediately before admission the headaches increased; she became delirious and had two convulsions. On her first admission she had pain over the vertex, the occiput and the back of the neck. When she moved her head, the pain extended to the sacrum. The neck was stiff. Lumbar puncture yielded bloody fluid under increased pressure. Studies of the blood and spinal fluid revealed nothing abnormal. The right foot became paralyzed, with atrophy. Within six months she was discharged from the hospital, in good condition. About one year later she was readmitted because of shooting pains in the left leg and dizziness. She had diminution of touch and pain sensation on the right side from the seventh thoracic level to the toes. The spinal fluid was clear. Almost eleven years later she was again admitted with complaints of weakness of the left side of the body and pain about the left ear, which radiated down the body, especially on the left side. There was no definite loss of motor power or sensation. Lumbar puncture yielded a clear fluid, with a cell count of 7 per cubic millimeter, a negative Wassermann reaction, a total protein content of 99.6 mg. and a sugar content of 64 mg. per hundred cubic centimeters. Bronchopneumonia developed and she died. Necropsy showed that the medulla was greatly displaced to the right by a firm, dark red mass;

28. Keegan, J. J., and Bennett, A. E.: Cerebral Aneurysm and Cortical Herniation, Arch. Neurol. & Psychiat. **26:** 36 (July) 1931.

29. Dial, D. L., and Maurer, G. B.: Intracranial Aneurysms, Am. J. Surg. **35:**2 (Jan.) 1937.

30. Maass, U.: Die Syphilis als haüfigste Ursache der Aneurysmen an der Gehirnbasis, Beitr. z. path. Anat. u. z. allg. Path. **98:** 307, 1937.

31. Boyd, L. J., and Werblow, S. C.: Coarctation of the Aorta, Dissecting Aneurysm and Aneurysmal Dilatation of the Left Vertebral Artery, Ann. Int. Med. **11:** 845 (Nov.) 1937.

32. Loder, K. J.: Aneurysm of Vertebral Artery, New York M. Coll. & Flower Hosp. Bull. **1:**62 (June) 1938.

33. Bassoe, P.: Aneurysm of the Vertebral Artery, Arch. Neurol. & Psychiat. **42:** 127 (July) 1939.

3.5 by 3 cm., which proved to be an unruptured aneurysm of the left vertebral artery. In the basilar artery, less than 1 mm. beyond the union of the two vertebral arteries, was a globular aneurysmal dilatation, 12 mm. wide. Within 5 mm. of the upper bifurcation of the basilar artery was a third, yellower, aneurysm, which was 1 cm. long and 4 mm. wide. A fourth, rust-colored, circular nodule was observed inside the bulb. All these aneurysms were unruptured, had thick walls and contained old clots. The subarachnoid hemorrhage, which occurred twenty-three years before, undoubtedly had been caused by rupture, with subsequent healing, of a similar aneurysm. The patient also had syphilitic aortitis and generalized arteriosclerosis. Bassoe also reported a second case of aneurysm occurring in a man 52 years of age. Five years before examination he had experienced several attacks of dizziness and severe headache, usually at night. Two years after the onset of these symptoms he noted numbness of the left side of the body, which persisted, and dragging of one foot. Five days before examination he had a severe vertiginous spell, which was followed by frequent clonic spasms of the extremities on the right side and difficulty in swallowing. He had a generalized convulsion. Examination revealed a Babinski sign bilaterally. The deep tendon reflexes in the lower extremities were increased, more on the left side than the right. Pain and temperature sensations were impaired on the left side of the body, except for the face. There was ataxia of the right hand. The right leg was slightly weak. Speech was thick. Lumbar puncture yielded clear spinal fluid. The Wassermann reaction was negative. The patient's condition improved, and he went to the Johns Hopkins Hospital for further study. Suspecting a tumor of the brain stem, Dr. Dandy explored the posterior fossa and encountered "a vascular aneurysm with a tremendous enlargement of the left vertebral artery." The wound was closed, and it was planned to ligate the vessel and remove the aneurysm later. However, the patient had more convulsions and died.

The cases of Dandy [34] and of Richardson and Hyland [35] illustrate the simulation of a neoplasm of the cerebellopontile angle by an aneurysm of the vertebral artery. The patient of Richardson and Hyland, a man aged 49, for ten years had suffered from a mental syndrome which had been diagnosed as dementia precox, the paranoid type. He had a history of tinnitus in the left ear for two years and frequent occipital headaches. The year prior to examination he had increasing deafness on the left side. For six months he had had numbness of the left side of the face, and for two months, nausea, diplopia, weakness of the left side of the face and unsteadiness of gait. Neurologic examination revealed paresis of the extremities on the left side. Horizontal nystagmus was present on left lateral gaze. There were clinical signs of palsies of the third, fifth, sixth, seventh and eighth cranial nerves on the left side. At operation a nodular tumor was observed in the left cerebellopontile angle, which after a hemorrhage was recognized as an aneurysm. The patient had a high postoperative fever, lapsed into coma and died. At necropsy a large, dumbbell-shaped, nodular aneurysm, measuring 5 by 3 by 2 cm., was seen on the anterolateral aspect of the left side of the pons; this mass filled the cerebellopontile angle and was firmly compressed against the sphenoid bone. The aneurysm was attached by a narrow neck to the trunk of the right vertebral artery at its junction with the basilar artery.

The left vertebral artery was small and threadlike. Dandy's [34] patient, a woman aged 63, presented the initial symptoms of progressive deafness and roaring in the left ear. One year after the onset of symptoms she had attacks of extreme vertigo, especially on quick change of posture, associated with nausea and vomiting. The deafness in her left ear increased, as did the roaring, and unsteadiness of gait developed. Operation revealed an aneurysm under the left eighth cranial nerve, which was stretched over the aneurysmal mass. The aneurysm was traced downward and observed to be continuous with the left vertebral artery.

Globus and Schwab [36] reported a case which also offered signs and symptoms suggestive of a midline tumor of the posterior fossa. In a woman aged 50 severe pain had developed on the left side of the neck eight years before. Dizziness occurred in an episodic fashion, associated with headache over the right supraorbital region. Just before her admission she had difficulty in swallowing and articulation, with generalized weakness. Examination showed bilateral papilledema and postneuritic atrophy, horizontal nystagmus in both lateral planes, deviation of the jaw to the left, paresis of the left extremities and a broad-based gait. The spinal fluid was clear and colorless, and the total protein content was 64 mg. per hundred cubic centimeters. Laryngoscopic examination disclosed palatal paralysis. Roentgenologic examination of the skull revealed nothing abnormal. Caloric tests suggested a lesion of the posterior fossa. A ventriculogram revealed considerable dilatation of both lateral ventricles, the right being slightly larger than the left; the third ventricle and the iter were visualized. Suboccipital exploration was considered, but the patient died suddenly. Necropsy revealed a large, bluish mass which compressed the inferior surface of the left cerebellar hemisphere, the upper half of the medulla and the pons. It seemed to extend into the foramen magnum. The mass was observed to be an aneurysm of the left vertebral artery, which measured 1.5 by 1 by 0.75 inch (3.8 by 2.5 by 1.9 cm.) and which, on subsequent study, proved to be due to proliferative endarteritis.

COMMENT

Of the 72 cases of aneurysm of the vertebral artery found in the literature, 35 were reported with sufficient historical and clinical data to make possible an analysis of the clinical features.

The age of onset of aneurysms of the vertebral artery varied from 2 to 69 years, but the majority of cases were observed in patients from 40 to 60 years of age. Of the 35 cases analyzed, 25 occurred in this age period. In 22 of the 35 cases with data concerning sex the patients were males and in 13 they were females.

The causes of intracranial aneurysm are generally given as congenital defect in the vascular walls, arteriosclerosis, syphilis, trauma and septic embolism. Arteriosclerosis undoubtedly is the chief cause in most instances, particularly in cases occurring in the older age groups. It was the most prevalent condition in this series of cases. There is some difference of opinion as to the frequency of syphilis as an etiologic factor.

34. Dandy, W. E.: Pathologic Changes in Ménière's Disease, J.A.M.A. **108**: 931 (March 20) 1937.
35. Richardson, J. C., and Hyland, H. H.: Intracranial Aneurysms, Medicine **20**: 1 (Feb.) 1941.

36. Globus, J. H., and Schwab, J. M.: Intracranial Aneurysms, J. Mt. Sinai Hosp. **8**: 547 (Jan.-Feb.) 1942.

In 5 reported cases of aneurysm of the vertebral artery the lesion was ascribed to syphilitic disease of the arteries. In 1 of these cases, described by Boinet,[19] an aneurysm of the left vertebral artery was associated with gummas of the brain and meninges. Hedinger[15] described a case of an unruptured aneurysm of the right vertebral artery in a syphilitic patient who had been hemiplegic for eight years. The aneurysmal sac revealed histologic evidence of syphilitic aortitis. Maass[30] described 2 cases of a small ruptured aneurysm of the vertebral artery in which death occurred during initial subarachnoid hemorrhage. The histologic evidence of syphilis in these cases is debatable. Bassoe[33] reported a case of saccular aneurysm of the left vertebral artery compressing the adjacent portion of the pons and medulla, with histologic evidence of syphilitic arteritis.

The part played in the formation and rupture of these aneurysms by congenital anomalies of vessels, congenital aneurysm, trauma, hypertensive disease and arteritis following embolism is difficult to evaluate from the cases reported.

Trauma as a cause cannot be established conclusively in this series of cases. Instances of aneurysm of the vertebral artery after fracture of the skull or injury to the head have been reported. Hedinger[22] recorded the case of a man who died suddenly of subarachnoid hemorrhage four years after a severe fall. The patient had experienced recurrent pain in the neck after the accident. Necropsy revealed a small ruptured aneurysm of the left vertebral artery. Dial and Maurer[29] recorded the case of a 2 year old child who died of sudden subarachnoid hemorrhage shortly after sustaining a fracture of the skull. A small ruptured aneurysm of the right vertebral artery was observed. However, the authors could not establish to their satisfaction whether the aneurysm was traumatic in origin or was due to a congenital defect. In the case reported by Morrow[24] and in that described in this paper there were histories of antecedent cranial trauma.

Clinical Features.—It is possible to classify aneurysms of the vertebral artery under two types, acute and chronic. In cases of both types death occurred frequently from rupture and subarachnoid hemorrhage. The number of deaths from this cause in the cases collected was 16.

Under the acute type may be placed the cases characterized by sudden death due to hemorrhage with no preliminary symptoms. These cases constitute a small group. Cases of the chronic type form a much larger group; they are characterized by a prolonged history, often with focal neurologic symptoms. The aneurysms in this category are of the large, unruptured type which persist for months or years and which rarely rupture to cause sudden death. Twenty-one of the cases studied fell in this group.

The nature of the symptoms produced by an unruptured aneurysmal mass of the vertebral artery depends on its location and size, its rate of expansion, the secondary changes which it may undergo and the pressure produced on the structures of the posterior fossa. It is easy to understand the variability of the symptoms and signs when one studies the course of the vertebral artery, coming into contact, as it does, first with the upper cervical portion of the cord, as it proceeds upward to enter the cranial cavity by way of the foramen magnum, and then with the side of the medulla and the basilar surface of the cerebellar hemisphere, and finally inclining toward the ventromedian line and, at the posterior border of the pons, joining its fellow artery to form the basilar artery.

The most frequent and striking symptom is suboccipital headache and nuchal pain, characterized by its episodic nature in most cases, although it may be persistent. The pain in the neck often radiates and is aggravated or precipitated by change in position of the head and neck. In many cases it is associated with generalized headache. This symptom was recorded in 15 cases of our series. It is not specific for aneurysm of the vertebral artery, but it is characteristic of an extramedullary expanding lesion of the high cervical region of the cord or the foramen magnum and of tumor of the posterior fossa.

Vertigo associated with nausea and vomiting occurs in most cases. Paralysis of the fifth to the twelfth cranial nerve is frequently encountered. Tinnitus and deafness occurred in 4 of the collected cases. Other early symptoms recorded were irritability, prolonged drowsiness, periodic headache, vague cerebellar and vestibular symptoms and symptoms suggesting increased intracranial pressure which defied localization. Papilledema was recorded in only 2 of the collected cases (Rindfleisch[16] and Globus and Schwab[36]).

Morrow[24] emphasized that aneurysms of the vertebral artery do not tend to rupture early. This fact probably accounts for the greater frequency of cases of the chronic type the symptoms of which suggest psychogenic disease. Most frequently the condition terminates in a complex suggesting slow medullary compression. The symptoms may exist for two months (Wichern[20]) or for more than a decade (Bassoe[33]), and the course of the illness tends frequently to be punctuated by acute episodes which leave few residual effects, as illustrated by the cases of Wells,[25] Keegan and Bennett,[28] Loder[32]

and Bassoe.[33] Eventually a well developed picture of medullary compression or sudden subarachnoid hemorrhage terminates the clinical course. Oppenheim [37] emphasized that the development of the disease is generally protracted and that the bulbar symptom complex does not as a rule come on suddenly, but is steplike in onset, sometimes becoming suddenly acute. Seizures appear repeatedly during the illness, characterized by nuchal rigidity, incoherent speech, paralysis of deglutition, dyspnea, changes in the pulse and, occasionally, mental confusion. The bulbar symptoms gradually subside, to recur with a new attack. In the intervals phenomena remain which are due to the irritation or the paralytic condition of one or of several bulbar nerves or to the effects of compression on the adjacent portion of the medulla, cerebellum or pons.

Unfortunately, in few cases have observations on the spinal fluid been recorded. In each instance in which it was noted the total protein content of the spinal fluid was elevated, the level ranging from 64 to 116 mg. per hundred cubic centimeters. In instances in which the aneurysm has not ruptured, the spinal fluid may be clear or xanthochromic. Other laboratory studies offer no clue as to the possible origin of the lesion. Ventriculograms reveal considerable dilatation of the ventricular system, such as is seen with any lesion in the posterior fossa which encroaches on the fourth ventricle.

A bruit was detected in only 1 case. Möser [11] heard a bruit on each side between the mastoid process and the vertebral column. Necropsy showed the aneurysm in the posterior fossa near the foramen magnum, in association with the left vertebral artery.

In the majority of cases the clinical picture may lead one to suspect a tumor of the brain or the high cervical portion of the spinal cord. In 10 of the collected cases the final clinical syndrome was that of a neoplasm of the posterior fossa. In 2 of the reported cases a typical history and signs of a neoplasm of the cerebellopontile angle neoplasm were presented (Richardson and Hyland,[35] Dandy [34]). The unruptured aneurysm may simulate an extramedullary neoplasm in the high cervical portion of the cord with extension through the foramen magnum. The cases reported by Bailey [21] and Barraud [38] are illustrative of this condition.

The clinical symptoms of vertebral aneurysm are not diagnostic before rupture. In cases of this type the clinical signs are due mainly to the pressure exerted on neighboring structures by the enlarging aneurysmal sac. Signs resulting from actual spontaneous subarachnoid hemorrhage in cases of aneurysm of this type are slight and are often absent during the clinical course. The patient frequently complains of pain in the back of the neck, which may radiate and which is made worse by movements of the head and neck. Compression of the cerebellum and medulla evokes the symptoms of incoordination and bulbar paralysis, which develop by easy stages or in a subacute manner. In addition, symptoms of irritation and paralysis of the basilar nerves appear. The fifth to the twelfth cranial nerve are most often involved. The spinal fluid may be clear or xanthochromic. The protein content of the spinal fluid is always elevated. The spinal fluid pressure may or may not be elevated. The syndrome envoked may simulate that of neoplasm of the posterior fossa, the region of the foramen magnum or the high cervical portion of the cord.

The exact diagnosis of an unruptured aneurysm of the vertebral artery during life is no more possible today than it was when Gull [39] stated, nearly eighty-five years ago that "although we may from the circumstances sometimes suspect the presence of aneurysm within the cranium, we have at least no symptoms upon which to ground more than a possible diagnosis."

SUMMARY

Large intracranial aneurysms of the vertebral artery are rare.

A clinical picture dominated by intermittent and long-standing symptoms of vague cerebellomedullary or pontile involvement and gradual compression of the medulla should suggest the possibility of aneurysmal dilatation of the vertebral arteries. This diagnostic consideration is especially pertinent in the presence of suboccipital headache and nuchal pain which may be aggravated by change in the position of the head.

The clinical picture may lead to a suspicion of tumor of the posterior fossa (cerebellomedullary or cerebellopontile), tumor in the region of the foramen magnum or neoplasm of the high cervical portion of the cord.

In cases of unruptured aneurysm there appears to be no specific sign or symptom which allows a preoperative differentiation between aneurysm of the vertebral artery and tumor.

Jefferson Medical College of Philadelphia.

37. Oppenheim, H.: Disease of the Nervous System, translated by E. E. Mayer, ed. 2, Philadelphia, J. B. Lippincott Co., 1904.

38. Barraud, A.: Sur un cas d'anévrisme de l'artère vertébrale gauche dans son pacours intrarachidien, Rev. de laryng. 57:375 (March) 1936.

39. Gull, W.: Aneurism of the Cerebral Vessels, Guy's Hosp. Rep. 5: 281, 1859.

ABSCESS OF THE MEDULLA OBLONGATA

REPORT OF A CASE

GEORGE D. WEICKHARDT, M.D., AND JAMES W. WATTS, M.D.

WASHINGTON, D. C.

Localization of an abscess in the medulla oblongata is rare. A rather complete survey of the literature shows that only 9 cases have previously been reported (table). Another case is here added to the list.

REPORT OF CASE

White man aged 34. History of intermittent discharge from right ear since childhood. Mastoiditis and facial paralysis (right side), relieved by simple mastoidectomy;

Physical Examination.—The patient appeared well nourished and healthy and did not seem acutely ill. The right eye was amblyopic. There was pronounced internal strabismus. The pupillary reactions were normal. There was no ptosis or nystagmus. The drum membrane of the right ear showed a plug of white debris over the area of the lateral process of the malleus. When this was removed, a thick, purulent secretion oozed out. Hearing was lost in this ear. There was no tenderness over the mastoid. The left ear was normal. The heart was normal, and the lungs were clear except for a few asthmatic wheezes. The deep tendon reflexes were equal

*Data on Cases of Abscess of the Medulla Reported in the Literature ***

Author	Age, Yr.	Sex	Site of Primary Infection	Position and Extent of Abscess	Motor Phenomena	Sensory Phenomena	Cranial Nerve Signs	Approximate Duration of Life Following Involvement of Central Nervous System
Abercrombie [8]	1½	M	Unknown	Medulla (central)	Hemiparesis (R)	None	None	3 mo.
Forget [4]	44	F	Unknown	Medulla; pons (R)	Convulsive movements of face (R)	None	VII (R)	5 days
Bircher [3]	44	M	Right forearm	Medulla; pons (R)	Hemiparesis (L)	Hemianalgesia (L)	V (R) VII (R) XII (R)	5 days
Eisenlohr [1]	43	M	Left lung	Medulla; C 1 C 2 (L)	Quadriplegia (L > R)	Hemianesthesia (L)	None	4 days
Schlesinger [6]	31	M	Prostate	Medulla (central)	Paraplegia (R > L)	Hyperesthesia of trunk	None	7 weeks
Dogliotti [2]	16	M	Thumb	Medulla; C 1 (R)	Quadriplegia	Hemianesthesia (L)	VII (R) XII (R)	24 days
Cassirer [5]	39	M	Appendix	Medulla; pons (R)	None	Hemianesthesia (L)	V (R) VI (R) VII (R)	8 days
Moniz [9]	Adult	M	Ear (?)	Medulla (R)	None	None	V (R) VII (R)	6 mo.
Norman [7]	43	M	Lungs	Medulla (central)	None	Hypesthesia of right arm	V (R) XII (L)	10 days
Weickhardt and Watts	34	M	Ear	Medulla; flocculus; pons	None	Impaired position sense (R)	V (R) VI (R) VII (R) VIII (R) IX (R) XII (R)	9 days

* The right side is indicated by R and the left side by L.

followed by recurrent paroxysms of meningitis. Persistence of symptoms, necessitating radical mastoidectomy. Signs of petrositis and dysfunction of ipsilateral cerebellar hemisphere. No cerebellar lesion disclosed by exploratory craniotomy. Focal meningitic complications and intramedullary abscess revealed at necropsy.

Anamnesis.—The patient first applied for treatment on Sept. 16, 1942 because of pain in the right ear. He told us that the ear had been draining intermittently since early childhood. He recalled having a fracture of the skull at the age of 10 years, but apparently there were no serious sequelae.

and lively on the two sides. No meningitic phenomena were recognized.

Serologic tests of the blood for syphilis gave negative results. Roentgenographic examination showed that the cells of the right mastoid were completely obliterated.

Clinical Course.—Intensive treatment with sulfonamide compounds produced no clinical improvement. On October 19 severe pain developed around the right ear, radiating to the forehead. Mastoidectomy was advised, but permission for operation was refused. On November 14 paralysis of the right side of the face developed. A simple mastoidectomy was immediately performed on the right side, and pus under pressure was released.

The postoperative course was uneventful for twenty-one days. On December 4 the patient began to complain of severe headache. The neck was somewhat rigid; Kernig's sign was elicited, and the temperature rose to 101.4 F. The facial paralysis had practically disappeared. The operative incision was nearly healed, but pus continued to drain from the auditory meatus. Examination of the spinal fluid showed 3,500 leukocytes per cubic millimeter (50 per cent lymphocytes and 50 per cent neutrophils), increased protein and no sugar. No organisms could be seen in the smear, and culture of the fluid was sterile. Treatment with sulfadiazine for a week led to complete disappearance of meningitic signs.

On Jan. 9, 1943 a second episode of meningeal irritation occurred. The mastoid incision at this time was well healed. The aural discharge persisted, although drainage seemed inadequate. Another spinal puncture yielded fluid the composition of which was essentially similar to that of the first specimen (2,000 cells per cubic millimeter, of which 75 per cent were neutrophils and 25 per cent lymphocytes; increased protein; 24 mg. of sugar per hundred cubic centimeters; a negative Kolmer reaction, and a colloidal gold curve of 000112222).

was paralyzed, and there was pronounced dysphagia. The protruded tongue deviated to the right. At this stage our diagnosis was osteomyelitis of the right petrous bone and diffuse purulent leptomeningitis. Abscess of the right cerebellar hemisphere was suspected.

On March 18 the cerebellar hemisphere was explored with the brain cannula. No abscess was encountered.

The patient's condition following the operation continued practically unchanged until 9 o'clock the following morning, when it was noted that respirations were rather shallow. An hour later he died suddenly and quite unexpectedly.

Necropsy.—A complete autopsy revealed that the internal organs were essentially normal. The brain showed no signs of increased intracranial pressure. The anterior surface of the right lobe of the cerebellum was densely adherent to the petrous pyramid. The dura here was thickened and granular. An attempt to sever the adhesions led to the discovery of an abscess cavity in the region of the cerebellopontile angle. This cavity contained several cubic centimeters of greenish yellow pus. The abscess extended into the substance of the brain stem, involving principally the right dorsolateral portion

Cross section through the medulla oblongata, showing abscess in the right dorsolateral portion. Weigert preparation.

A smear and culture again showed no organisms. For a second time the signs of meningitis responded to sulfadiazine therapy.

The patient was comfortable until January 31, when an abscess appeared in the mastoid scar. The ear continued to drain freely. A radical mastoidectomy was carried out on February 10. The postoperative course was satisfactory for twenty-four days. On March 6 signs of meningitis appeared for a third time, together with weakness of the right side of the face. Aural discharge continued undiminished. Repeated spinal punctures failed to reveal a causative organism. Within a few days the patient began to complain of distressing dizziness. The facial paralysis became complete. On March 10 the patient showed a strong tendency to fall to the right on attempting to stand. There was horizontal nystagmus on his gazing far to the right or to the left. Speech showed a gradually increasing bulbar quality. On March 12 he showed complete anesthesia over the distribution of the right trigeminal nerve, with absence of the corneal reflex. The right abducens nerve was paralyzed. The right arm and leg showed slowly increasing ataxia. The speech difficulty became more pronounced. The following day the right half of the palate

of the medulla oblongata and the right flocculus. It also extended upward into the lower portion of the pons. No other focal lesion was observed in the brain. The petrous portion of the right temporal bone was soft and necrotic. In its substance were two irregular sequestrums. Necrosis extended for a short distance into the squama. The anatomic diagnosis was osteomyelitis of the right temporal bone and abscess of the brain stem. Unfortunately, no bacteriologic examination was made.

Histopathologic Study (Dr. Walter Freeman).—A cross section through the medulla oblongata (figure) showed that the abscess occupied its extreme lateral portion and compressed medially such structures as the fasciculus solitarius, the descending root of the trigeminal nerve and the inferior olivary body. The corpus restiforme at this level was almost completely destroyed. The abscess was not clearly walled off. There was obvious extension into the surrounding tissues, as evidenced by collections of leukocytes around blood vessels at some distance from the abscess cavity. The Laidlaw stain showed moderate proliferation of connective tissue surrounding the abscess cavity, but nowhere did it approach the formation of an actual wall. The Bodian stain showed that the axis-cylinders in the immediate

vicinity of the abscess were swollen to large proportions and tended to undergo liquefaction.

Microscopic examination of the petrous pyramid showed small portions of necrotic bone in a matrix of granulation tissue heavily infiltrated with leukocytes.

COMMENT

Abscesses of the medulla oblongata reported in the literature present a remarkably heterogeneous clinical picture. They are alike only in being invariably fatal. Slight variations in position and size of medullary lesions produce remarkably different syndromes. Abscesses in the brain stem, furthermore, show a tendency to form elongated cavities, so that several levels, or segments, are likely to be involved. Thus, of the 10 cases encountered, the abscess was limited to the medulla oblongata in only 3. In the cases of Eisenlohr [1] and Dogliotti [2] the lesion could be followed into the upper cervical segments of the spinal cord, while in the cases reported by Bircher,[3] Forget [4] and Cassirer [5] and in our case it extended upward into the pons. In Schlesinger's [6] case there were two abscesses: an elongated lesion involving the cervical and upper dorsal segments of the spinal cord and a pea-sized intramedullary abscess at the level of the pyramidal decussation. There may be other intracranial complications (as in our case).

In 6 of the cases reviewed the abscess was of metastatic origin, with distribution of primary foci as follows: abscess of the forearm [3];

abscess of the lung [1]; abscess of the prostate, leading to purulent meningitis [6]; paronychia of the thumb [2]; perityphlitis, with abscesses in the liver and lungs,[5] and apical pulmonary tuberculosis, with secondary infection.[7] The lesion in the medulla oblongata of a child described by Abercrombie [8] as an abscess has been regarded by most reviewers as a tuberculoma. Forget's [4] report contains no discussion of pathogenesis. In the case of Moniz,[9] as in our own, invasion of the brain stem was apparently due to direct extension of purulent otitis.

Death is due usually to compression of the medullary centers. In the majority of cases only a few days intervened between onset of neurologic complications and fatal termination. A much longer time elapsed in the cases of Abercrombie, Schlesinger and Moniz.

In our case the infection evidently extended along the petrous portion of the temporal bone and through the dura into the region of the cerebellopontile angle. The first clinical sign to indicate intramedullary abscess formation was the appearance, nine days before death, of hemiataxia. This was evidently due to destruction of pathways in the inferior cerebellar peduncle. The bulbar signs which followed were attributed at the time to the pressure of an expanding cerebellar lesion rather than to invasion of the medulla. The fifth and sixth nerves were evidently involved in the petrosal osteomyelitis. It is felt that the patient had no chance for recovery even if it had been possible to drain his abscess.

SUMMARY

A case of abscess of the medulla oblongata reported here is unique in that origin from infection of the middle ear is clearly demonstrated.

638 Eighth Street N. E.
1028 Connecticut Avenue N. W.

1. Eisenlohr, C.: Ueber Abscesse in der Medulla oblongata, Deutsche med. Wchnschr. 18:111 (Feb. 11) 1892.

2. Dogliotti, A.: Ascesso del midollo allungato da stafilococchi, Gazz. med. di Torino 50:841 (Oct. 26) 1899.

3. Bircher, H.: Beobachtungen zur Pathologie des Gehirns: Abscess in Medulla oblongata und Pons, Cor.-Bl. f. schweiz. Aerzte 11:102 (Feb. 15) 1881.

4. Forget, C.: Note sur les rapports des symptomes avec les lésions encéphaliques, Union méd. 4:366 (July 27) 1850.

5. Cassirer, R.: Ueber metastatische Abscesse im Centralnervensystem. Isolierter metastatischer Abscess im Pons und in der Medulla oblongata, Arch. f. Psychiat. 36:153 (Aug.) 1902.

6. Schlesinger, H.: Ueber Rückenmarksabscess, Arb. a. d. Inst. f. Anat. u. Physiol. d. Centralnervensyst. a. d. Wien. Univ. 2:114, 1894.

7. Norman, H. B.: Abscess of the Medulla Oblongata Associated with Chronic Pulmonary Tuberculosis, Brit. M. J. 1:403 (March 15) 1941.

8. Abercrombie, J.: Pathological and Practical Researches on Diseases of the Brain and Spinal Cord, ed. 3, Edinburgh, Maclachlan, Stewart & Co., 1836, p. 103.

9. Moniz, E.: Abcès isolé du bulbe, Rev. d'oto-neuro-opht. 12:568 (Oct.) 1934.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Physiology and Biochemistry

THE EFFECT OF ELECTRICALLY AND CHEMICALLY INDUCED CONVULSIONS ON CONDITIONED REFLEXES. M. KESSLER and E. GELLHORN, Am. J. Psychiat. **99**: 687 (March) 1943.

Kessler and Gellhorn produced a conditioned response to the sound of a bell in 18 rats and then inhibited the response by failing to reenforce it with the unconditioned stimulus (electric shock). The induction of convulsions by either metrazol or electric shock restored temporarily the inhibited conditioned response.

FORSTER, Philadelphia.

THE PAIN THRESHOLD IN MAN. JAMES D. HARDY, HAROLD G. WOLFF and HELEN GOODELL, Am. J. Psychiat. **99**: 744 (March) 1943.

Hardy, Wolff and Goodell devised an apparatus for the graduated production of thermal pain and studied the variations in the pain threshold. The threshold thus measured was found to be relatively constant in the same subject and to be independent of age, sex, emotional state and fatigue. Despite the constancy of the pain threshold, the authors found that the "alarm" reaction threshold varied widely in the same subject over a period of two months. The pain threshold was dependent only on the strength of the stimulus, and not on the area involved. The effects of lesions of the peripheral and the central nervous system were studied, the authors concluding that lowered pain threshold is never due to structural disease. Structural disease of the nervous system, if it causes any alteration, always raises the threshold.

FORSTER, Philadelphia.

THE EQUILIBRIUM BETWEEN CALCIUM AND CEPHALIN IN VARIOUS SYSTEMS. N. DRINKER and H. H. ZINSSER, J. Biol. Chem. **148**: 187, 1943.

As cephalin can be shown to bind appreciable amounts of calcium, both alone and in the presence of protein, evaluation of the cephalin content of normal and pathologic serums may serve to clarify the role of plasma proteins in the regulation of calcium ion concentration. In the concentrations present in normal plasma, it would seem that 30 to 40 per cent of the bound calcium may be held in nondiffusible form by cephalin.

PAGE, Indianapolis.

OBSERVATIONS ON THE FUNCTIONAL DEVELOPMENT OF THE FOETAL BRAIN. JOSEPH BARCROFT and DONALD H. BARRON, J. Comp. Neurol. **77**: 431 (Oct.) 1942.

Barcroft and Barron studied the normal behavior of 200 sheep fetuses ranging in age from 32 to 147 days with special reference to respiratory movements and to righting and postural movements. Movements of the diaphragm and intercostal muscles were first observed in a fetus 38 days old. The respiratory movements pass through four phases of development: (1) a phase in which the diaphragm contracts with the muscles of the neck, and only with them; (2) a phase in which contractions of the diaphragm are dependent on muscular activity but are not linked to the activity of any specific group of muscles; (3) a phase in which the respirations outlast the stimulus or body activity, and (4) a phase of inhibition. Righting and postural efforts develop in the following order: tonic neck reflexes on the legs; head righting; compensatory movements of the eyes, and body righting. A study of these features was made in fetuses with lesions in the brain stem ranging from the upper cervical portion of the cord to the cerebral cortex. The operations were performed on fetuses between 40 and 70 days of age, and the postoperative study was made on fetuses between 54 and 132 days of age. The region of the brain responsible for the first two phases of respiration is in the lower portion of the medulla, that for the third phase in the pons and that for the fourth phase in the caudal half of the midbrain. The region responsible for the tonic neck reflexes on the legs is the upper cervical portion of the cord and the lower part of the medulla, and that for head righting is in the pons and the lower part of the midbrain. Compensatory movements of the eyes and body righting occur only if the brain stem behind the diencephalon and spinal cord are intact.

ADDISON, Philadelphia.

PERIODICITY IN THE DEVELOPMENT OF THE THRESHOLD OF TACTILE STIMULATION IN AMBLYSTOMA. C. E. COGHILL and R. W. WATKINS, J. Comp. Neurol. **78**:91 (April) 1943.

Coghill and Watkins report the results of tactile stimulation of embryos selected from the same clutch, and therefore of approximately the same age. The embryos were stimulated by the touch of a hair. The point touched and the degree of the touch were controlled under a stereobinocular microscope, mounted so that it could be moved from one dish to another without disturbing the specimens. By this method continuous observation of developing larvae of Amblystoma from first motility to full-swimming stages was possible. There was a pronounced periodicity in the development of sensitivity to light touch until the minimum threshold was reached. This periodicity involved the receptors and was of endogenous origin. It was not attributable to fatigue.   ADDISON, Philadelphia.

HOMOLATERAL REFLEX EXAGGERATION AFTER BRAIN-STEM LESION. FRED A. METTLER and FREDERICK T. ZIMMERMAN, J. Comp. Neurol. **78**: 113 (April) 1943.

Lesions were placed in the brain stem of 6 cats in regions not part of the corticospinal system, as well as in different parts of the corticospinal tract. In 2 cats the lesion extended from the rostral part of the medial geniculate body to the level of the superior olive; in 1 cat the brachium conjunctivum was destroyed, and in 3 cats the brachium pontis was severed. Exaggeration of the knee jerk was not related to damage of the pyramid, substantia nigra, brachium pontis or brachium conjunctivum. Lesions of the tegmentum evoked inequality of the knee jerk. If the lesion was below the level of the red nucleus, the more active reflex was homolateral; if it was rostral to the red nucleus, the more pronounced reflex was contralateral. Such lesions appear to interfere with extrapyramidal mechanisms in the telencephalon.

ADDISON, Philadelphia.

INNERVATION AND "TONUS" OF STRIATED MUSCLE IN MAN. EDMUND JACOBSON, J. Nerv. & Ment. Dis. **97**: 197 (Feb.) 1943.

Jacobson challenges the contention of Hoefer that the latter has measured slight states of muscular contraction in man for the first time and believes that certain of the records on which Hoefer based his conclusions were wrongly interpreted. The failure of Hoefer to record action potentials from leg muscles during standing is attributed to lack of delicacy of the recording system employed, which had a sensitivity of 3 mm. per hundred microvolts. Using his own, more sensitive, instruments, Jacobson found action potentials recorded from the leg muscles of 10 standing subjects. He states, also in opposition to Hoefer, that the string galvanometer records fully as sensitively as the cathode ray oscillograph and that it can be employed to record "brief single motor unit discharges." Although it may be true that normal muscle at rest receives no nerve impulses, Hoefer could not so conclude from his recordings because of their insufficient sensitivity.   CHODOFF. Langley Field, Va.

INVESTIGATION OF EPILEPTIFORM ATTACKS PRODUCED BY SUDDEN COOLING OF FROG SPINAL CORD. M. OZORIO DE ALMEIDA, J. Neurophysiol. **6**: 73 (March) 1943.

De Almeida found that sudden chilling to below 0 C. of the isolated spinal cords of North American frogs failed to produce epileptiform attacks. This was contradictory to the results obtained with South American frogs. In North American frogs attacks could be induced by cooling the cord to below 0 C. with agents such as ethyl chloride or solid carbon dioxide. Preliminary warming of the cord or injection of caffein facilitated the induction of seizures. Direct application of a concentrated solution of sodium chloride produced seizures in both North American and Brazilian frogs. De Almeida compared the effect of chilling the spinal cord in Rana catesbyana, a North American species, both in frogs adapted to North American temperatures and in those of the same species adapted to Cuban temperature for twenty years. In the latter group seizures could be induced. He concludes that the convulsive reaction of the nervous system changes slowly and progressively under the action of temperature.

FORSTER, Philadelphia.

EFFECT OF HYPOTHALAMIC LESIONS ON ELECTRICAL ACTIVITY OF CEREBRAL CORTEX. S. OBRADOR, J. Neurophysiol. **6**:81 (March) 1943.

Obrador studied the effect in 20 cats of lesions of the hypothalamus on the spontaneous electrical activity of the cortex. Lesions of the hypothalamic and basal portions of the brain produced complete abolition of the electrical activity. Lesions of the thalamus produced a similar response. On the basis of these studies and the anatomic evidence available, Obrador

concludes that the hypothalamus may influence the cerebral cortex through its thalamic connections. Complete section of the midbrain failed to alter significantly the electrical activity of the cortex. FORSTER, Philadelphia.

SPECIFIC EXCITABILITY OF THE ENDPLATE REGION IN NORMAL AND DENERVATED MUSCLE. STEPHEN W. KUFFLER, J. Neurophysiol. 6:99 (March) 1943.

Kuffler studied the properties of the end plate and the end plate-free region in single nerve-muscle preparations of the adductor longus of the Australian frog. Acetylcholine, nicotine and caffeine depolarized the muscle membrane at the end plate region and so induced impulses. They did not depolarize end plate-free portions of the muscle or set up impulses there. Potassium initiated impulses only in the end plate region, but no difference could be detected in its depolarizing effect at or off the end plate. Curarine opposed the depolarization and excitation caused by all the drugs with the exception of potassium. In chronically denervated muscles the sensitivity of the end plates to acetylcholine, nicotine and caffeine was increased. In these preparations, also, depolarization was limited to the end plate region. FORSTER, Philadelphia.

FUNCTIONAL ORGANIZATION OF TEMPORAL LOBE OF MONKEY (MACACA MULATTA) AND CHIMPANZEE (PAN SATYRUS). PERCIVAL BAILEY, GERHARDT VON BONIN, HUGH W. GAROL and WARREN S. McCULLOCH, J. Neurophysiol. 6:121 (March) 1943.

Bailey, von Bonin, Garol and McCulloch studied the functional organization of the temporal lobe in the monkey and in the chimpanzee by observing the changes in electrical activity produced by various stimuli. They found that the functional organization was the same in the two species. In both species the lobe was divisible into an acoustic and a temporal sector. The acoustic sector was composed of areas 41, 42 and 22. Stimulation of each of these areas caused spikes to appear in each of the others. The temporal sector was composed of areas 21, 20 and 38, each of which "fired" only locally on strychninization. In the macaque a temporopolar area was demonstrated. Commissural connections between the two temporal sectors are restricted to area 21 and probably occur through the anterior commissure. FORSTER, Philadelphia.

LONG ASSOCIATION FIBERS IN CEREBRAL HEMISPHERES OF MONKEY AND CHIMPANZEE. PERCIVAL BAILEY, GERHARDT VON BONIN, HUGH W. GAROL and WARREN S. McCULLOCH, J. Neurophysiol. 6:129 (March) 1943.

Bailey, von Bonin, Garol and McCulloch employed the method of physiologic neuronography in determining the long association fibers in the cerebral hemispheres of the monkey and the chimpanzee. Application of strychnine to area 8 (Brodmann) produced spiking in both ipsilateral and contralateral area 18. Strychninization of ipsilateral area 18 also produced spikes in contralateral area 18. The relayed spike was retarded. Strychninization of area 18 also produced spiking in area 20. Strychninization of area orbitalis agranularis (area 47 of Brodmann, FFA of von Economo) produced well defined strychnine spikes in the anterior portion of the temporal lobe. In none of these pathways could strychnine spikes be sent in the reverse direction. FORSTER, Philadelphia.

Diseases of the Spinal Cord

A CASE OF EPIDERMOID TUMOR OF THE SPINAL CORD. ROBERT L. CRAIG, Surgery 13:354, 1943.

Craig's revision of the list of cases of dermoid and epidermoid tumors of the vertebral canal which Boldrey and Elvidge collected from the literature, together with his own report of a case gives a total of 43 cases of such tumors. Craig's case was that of a subpial epidermoid in the lumbosacral portion of the cord associated with spina bifida of the first sacral segment. He explains a sensory level extending to the eleventh thoracic dermatome by the presence of associated arachnoiditis, observed at operation. The poor results obtained on attempted removal of tumors of this type from an intramedullary location are believed to occur because of innumerable folds into which the basement membrane of the tumor is thrown and the consequent enmeshing of the parenchyma.

The series as finally revised contains 20 probable cases of epidermoid and 23 probable cases of dermoid tumor. Of the epidermoids, half were intramedullary and half extramedullary. The dermoids were more often extramedullary, and occasionally extradural. Preoperative diagnosis of these tumors is not always possible, but the association of a cutaneous dimple or a discharging sinus in the middle of the back or the presence of spina bifida should suggest

cent. Severe and persistent extension contractures usually developed in patients who had been maintained in splints for some time. Evidence of circulatory disturbances, which result not only in impairment of circulation but in changes in the bone in the segmental area of the musculature involved, was most definite in patients with the most severe involvement of the surrounding musculature and contracture. As early as two or three months after the onset of poliomyelitis there was definite loosening of the ligamentous reenforcements of the severely involved joints, especially of the ankle and the shoulder. These changes occurred particularly in patients who had been wearing airplane splints and in whom a constant upward pressure on the shoulder joint was at work. From these observations it must be assumed not only that muscle is involved but that ligaments, bones and tendons play a part in the pathologic changes of anterior poliomyelitis. Extensive involvement of the musculature of the trunk was observed in more than half the patients. It was difficult to correlate the contractures of single groups of muscles because of the widespread and spotty nature of the paralysis. Since making these observations, the authors have tried to overcome the condition at its inception. They remove the splint for an hour twice a day and let the patient lie on his side with his hips and knees flexed. This is likely to loosen the contracture of the back, and there is no evidence that it produces contractures of the knee or hip. Miss Kenny has emphasized the fact that the patient must be reeducated to the use of the individual muscle; her suggestions for individual muscle training have been adopted, and certain departures from the old time orthodox treatment have been necessary. However, all fixation or immobilization should not be abandoned. Limbs that are unstable in their joints, whether or not they have recovered from the paralysis, must be supported. When walking or standing is resumed, apparatus for this support should not be used beyond the point at which static instability makes it necessary. When the soundness of the newer clinical observations on infantile paralysis is established, the application of common sense and of general biologic principles will free the treatment of poliomyelitis from orthodoxy and radicalism.

                                                                        J. A. M. A.

TESTOSTERONE THERAPY OF MALE EUNUCHOIDS: SUBLINGUAL ADMINISTRATION OF TESTO-
    STERONE COMPOUNDS. H. LISSER, R. F. ESCAMILLA and L. E. CURTIS, J. Clin. Endocrinol.
    2:351 (June) 1942.

According to Lisser and his associates, 5 typical eunuchoids whose improvement had previously been successfully maintained by parenteral implantation and/or oral administration of testosterone continued in their improved status with sublingual use of testosterone. With only 1 of the 5 patients was less testosterone required when given sublingually than when given orally. The patients preferred swallowing tablets to dropping a solution under the tongue. Four hypogonadal patients with no previous testosterone therapy were subjectively and objectively benefited from the sublingual administration of testosterone compounds. Larger oral doses of methyl testosterone would have been required to accomplish equivalent results. When administration was sublingual, free testosterone was more effective than methyl testosterone or testosterone propionate. The androgen to be used was dissolved in propylene glycol so that 0.2 cc. contained 5 mg. of the testosterone compound.   J. A. M. A.

STUDIES ON THE USE OF REFRIGERATION THERAPY IN MENTAL DISEASE WITH REPORT OF
    SIXTEEN CASES. DOUGLAS GOLDMAN and MAYNARD MURRAY, J. Nerv. & Ment. Dis.
    97:152 (Feb.) 1943.

Goldman and Murray used refrigeration in treatment of 16 patients with mental disease, including schizophrenia and involutional and manic-depressive psychoses. After each patient had received a barbiturate preparation to induce initial anesthesia, he was placed in a cabinet, the temperature of which was kept between 30 and 60 F. Pentobarbital sodium proved to be the most useful anesthetic, not only in permitting the patient to be packed in ice without discomfort but in paralyzing the normal temperature-regulating mechanism. The body temperature was lowered to 88 or 90 F. by initial application of the ice and was maintained at 85 to 86 F. within the cabinet by keeping the latter at a level of 55 to 60 F. Intensive nursing care and oral and intravenous feeding were necessary during treatment. The return to normal temperature required three to eight hours. The state of consciousness during the treatments varied from complete loss to relative alertness. The physical changes noted during refrigeration were decreased tendon reflexes, diminished pupillary reflexes and abolition of coughing, micturition and defecation. Changes in the rate and rhythm of the heart and irregularities in respiration were usually indicative of trouble. Changes noted in the blood were: (1) a variable degree of hemoconcentration; (2) a tendency toward lowering of the sugar content; (3) nitrogen retention; (4) a lowered carbon dioxide–combining power, and

gives the best results by preventing the development of end bulbs and adhesions for at least a year. Alcohol is relatively ineffective, while other fixatives occupy an intermediate position. The authors advocate the clinical application of these experimental results.

MALAMUD, Ann Arbor, Mich.

Treatment, Neurosurgery

THE EFFECT OF BENZEDRINE [AMPHETAMINE] SULFATE ON MIGRAINE. JACQUES S. GOTTLIEB, Am. J. M. Sc. **204**:553 (Oct.) 1942.

Gottlieb studied the effectiveness of amphetamine sulfate in treatment of 25 patients suffering from typical migraine. If the patients reported to the hospital during an attack, the drug was administered intravenously in doses of 3 to 20 mg. After their responses to intravenous medication were tested, patients were advised to take the drug orally in 10 to 40 mg. doses at the beginning of an attack. Eighteen received amphetamine sulfate intravenously from one to seven times for the relief of their attacks of migraine. Twelve (67 per cent) consistently obtained complete relief from their attacks in from seven to forty-five minutes. Most of the patients felt brighter and no longer fatigued. Medication administered orally was not as successful as when given intravenously. Eight patients (36 per cent) of the group obtained relief or had their paroxysms aborted in thirty to sixty minutes. Amphetamine sulfate was selected because it is a sympathomimetic compound with a prolonged action. It also decreases the amplitude of the pulsations of the cranial arteries.

MICHAELS, Boston.

THE EFFECT OF POTASSIUM THIOCYANATE ON THE OCCURRENCE OF MIGRAINE. DAVID E. ENGLE and CHARLES O. EVANSON, Am. J. M. Sc. **205**:697 (Nov.) 1942.

Engle and Evanson studied the effects of potassium thiocyanate on 13 patients with migraine. The average period of observation for each patient was eleven months. Patients who had attacks of migraine as frequently as three times per month, or who had coexisting hypertension, were instructed to take potassium thiocyanate to the amount of 6 grains (0.39 Gm.) daily for three days, and then 3 grains (0.19 Gm.) daily. Patients who had attacks of migraine less frequently than three times per month, and who could foretell the onset of an attack, were advised to take 6 grains of potassium thiocyanate when an attack seemed imminent. Twelve of the thirteen patients received substantial relief from migraine while taking the drug. The levels of thiocyanate in the blood which are effective against migraine are substantially lower than those generally considered to be most effective in the treatment of hypertension. The authors conclude that potassium thiocyanate properly administered is effective in reducing the frequency and severity of migraine headache.

MICHAELS, Boston.

EVALUATION OF CONTINUED THERAPY WITH PHENYTOIN SODIUM. LEON J. ROBINSON, Am. J. Psychiat. **99**:231 (Sept.) 1942.

Robinson studied the effects of administration of phenytoin sodium (dilantin) over long periods in 221 hospitalized patients with epilepsy. The patients had been treated with phenytoin sodium alone for as long as thirty to thiry-six months and with phenytoin sodium combined with phenobarbital for as long as thirty-eight or forty-one months. The results of therapy are as follows:

Drug	No. of Patients	Time, Mo.	Reduction of Seizures, % Marked	Moderate	None
Phenobarbital	93	5-44	15	20.4	64.5
Phenytoin sodium	41	3-33	39	24.3	36.5
Phenytoin and phenobarbital	104	....	28.8	21.1	49.9

Robinson noted, further, that some patients who at first did not respond to anticonvulsive therapy did so after a time. The converse was likewise true. Salutary effects other than relief from seizures are pointed out. The average dose of phenytoin sodium was found to be 4½ grains (0.3 Gm.).

FORSTER, Boston.

RECENT CHANGES IN CONCEPT OF TREATMENT OF POLIOMYELITIS. A STEINDLER and others, Arch. Phys. Therapy **23**:321 (June) 1942.

The physiologist states that the passage of a muscle through its complete range of motion at frequent intervals enhances, rather than retards, recovery by stimulation of the venous circulation and lymphatic passages to the affected members. During the 1940-1941 epidemic of poliomyelitis in Iowa, Steindler and his associates studied 200 patients particularly from the standpoint of the development of contractures, which took place in approximately 25 per

THE TREATMENT OF CEREBRAL CONTUSION. L. ROGERS, Brit. M. J. **1**:151 (Feb. 6) 1943.

Rogers calls attention to a method of treatment of cerebral contusion following "closed" injuries to the head which he states is theoretically, experimentally and clinically sound, and which consistently results in recovery without complications. He points out that the brain reacts to severe injury by attempting to increase its volume and that this expansion is limited by the meninges, the cerebrospinal fluid and the skull. Excessive swelling of the injured brain results in ischemia and necrosis. To provide room for expansion of the brain Rogers advocates removal of cerebrospinal fluid by dehydration measures. Dehydration is produced by the slow and gentle administration of retention enemas of 6 ounces (177 cc.) of a 30 per cent solution of magnesium sulfate in water every six hours; the fluid intake by mouth is restricted. The direct removal of cerebrospinal fluid by repeated lumbar puncture is not discussed.

The method has been used in the treatment of 550 patients with head injuries. Of these, 25 died, the majority soon after admission. There was a conspicuous absence of immediate and late complications. Not one of the 525 remaining patients required readmission for a "postconcussional" state or for any other complication.   ECHOLS, New Orleans.

EXPERIENCES IN THE TREATMENT OF DEPRESSIVE STATES BY ELECTRICALLY INDUCED CONVULSIONS. O. W. S. FITZGERALD, J. Ment. Sc. **89**:73 (Jan.) 1943.

Fitzgerald treated 150 patients with psychotic depressions, with the following results: (1) 117 patients (78 per cent) were discharged as recovered and continued in their home environment; (2) 6 patients (4 per cent) were discharged as improved; (3) 15 patients (10 per cent) remained in the hospital, and (4) 12 patients (8 per cent) were discharged but had a relapse and were readmitted to the hospital.

The average number of convulsions per patient was seventeen, regardless of the patient's age or the duration of the illness. The chances for recovery were unaffected by the duration of the illness up to the limit of three years, after which they diminished.

A six month period of observation by a social worker shows that 63 of the 85 patients discharged were known to be normal and usefully employed; 5 were unable to adjust; 9 were readmitted to hospital, and the condition of the rest could not be adequately evaluated.

The author suggests convulsions be given every day for a total of seven or eight treatments in order to make certain the patient is beyond the restless and agitated state.

M. M. PEARSON, Philadelphia.

CATAMNESIS OF PATIENTS WITH DEMENTIA PRAECOX SUBMITTED TO INSULIN THERAPY. A. P. QUARANTA, Rev. argent. de neurol. y psiquiat. **6**:109 (June) 1941.

In 1937 Quaranta resorted to insulin therapy in 41 cases of dementia praecox of different clinical forms and periods of duration. The duration was six months or less in 16 cases, one year or less in 12 cases and more than a year and a half in 17 cases. There were 17 cases of complete remission in the whole group, which corresponded to 10 out of 16 cases in the first group, 3 out of 12 in the second group and 4 out of 17 in the third group. Patients with a complete remission were observed for four years, by the end of which, in 1941, the remission lasted in 10 patients. Three patients had recurrences and are again under neuropsychiatric care. Four had recurrences but carried on a life which was compatible with their stay at home. All the 10 patients with permanent remissions were in good physical and mental condition, and were able to work. The author advises application of insulin therapy in cases of dementia praecox. The earlier the administration of the therapy, the better and more certain the results.   J. A. M. A.

TREATMENT OF CEREBROSPINAL SYPHILIS. J. MADSEN, Ugesk. f. læger **103**:1419 (Nov. 6) 1941.

Madsen says that lumbar puncture should be made in all cases of syphilis at the end of the septicemic period, or as a rule from three to six years after the infection. Normal spinal fluid in the latent period seems to exclude the later occurrence of neurosyphilis. If changes in the spinal fluid are found in this period, antisyphilitic treatment is justifiable, but if the spinal fluid does not become normal in the course of several months malaria treatment should be instituted. If signs of cerebrospinal syphilis are already present, for example, the Argyll Robertson symptom, a normal spinal fluid does not testify against an active inflammatory process in the nervous system, and in the author's opinion malaria treatment is indicated. A negative Wassermann reaction does not exclude cerebrospinal syphilis. If, without demonstrable cause, neurasthenic symptoms appear in a previously well

(5) a moderate drop in the chloride level. The chief complications were injuries to the skin from ice and infections of the respiratory tract, the latter being responsible for the 2 deaths which occurred during the treatment.

The results of treatment were disappointing. Except for transient, incomplete improvement in a few patients, no discernible results were noted. The authors have suspended the treatment in view of the considerable risk and the lack of benefit.   CHODOFF, Langley Field, Va.

CEREBROSPINAL FEVER TREATED BY CHEMOTHERAPY. G. E. HARRIES, Brit. M. J. 2:423 (Oct. 10) 1942.

Harries reports a series of 500 cases of cerebrospinal fever in which chemotherapy without intrathecal injection of serum was employed. The gross mortality rate was 8.6 per cent. When patients who died within the first twenty-four hours after admission were excluded, the mortality rate was 4.8 per cent. More males were affected than females. Most of the patients with this disease were between the ages of 15 and 25.

Harries proposes the following classification of cerebrospinal fever: meningococcic septicemic type, meningitic type and encephalitic type. Of particular diagnostic value in recognition of this condition are nuchal rigidity, purpuric eruptions, herpes, absence of photophobia and, in infants, a depressed fontanel. Sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) was given by mouth to 471 patients and sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) to the remaining 29 patients. Harries observed that sulfathiazole appeared to be as effective as sulfapyridine in promoting recovery and was less likely to produce nausea and vomiting. No patient was considered out of danger until the sugar content of the cerebrospinal fluid had returned to normal. For comatose patients tablets were crushed and given in nasal feedings. To patients who were severely ill the sodium salt of sulfapyridine was given intravenously. Fluids were forced in all cases. In patients with the acute fulminating form desoxycorticosterone acetate was given intramuscularly and 30 to 60 cc. of meningococcus antitoxin was administered intravenously. To all patients dextrose was given freely and a little table salt was added to the diet. Of the strains of meningococci cultured, 93 per cent belonged to group 1.

ECHOLS, New Orleans.

TREATMENT OF SHOCK BY DIRECT ACTION OF THE VEGETATIVE NERVOUS CENTERS. LENA C. STERN, Brit. M. J. 2:538 (Nov. 7) 1942.

On the basis of experimental study, Stern advocates injection of potassium phosphate into the cisterna magna in the treatment of the last phase of traumatic shock. In this phase there are a fall in tone of the sympathetic and a rise in tone of the parasympathetic nervous system. The potassium phosphate diffuses through the intraventricular fluid and acts directly on the vegetative nervous centers to increase sympathetic and inhibit parasympathetic activity. The usual methods of combating shock by the injection of chemicals into the circulation are generally ineffective because the hematoencephalitic barrier prevents them from reaching the vegetative centers of the brain. The dose of the shock remedy advocated is 1 cc. of a solution of potassium phosphate in a concentration of $\frac{1}{6}$ gram molecule with a p_H of 7.6.   ECHOLS, New Orleans.

PHYSICAL TREATMENT OF ACUTE WAR NEUROSES. W. SARGANT, Brit. M. J. 2:574 (Nov. 14) 1942.

Physical methods of treatment aid in shortening the period of total disability in many cases of acute war neuroses. The aim of physical treatment is "to bolster up the constitution so that unavoidable stresses are better tolerated by the individual." Heavy sedation, given as early as possible, is most beneficial in management of the acute panic state. When the neurotic symptoms persist for a week or longer, the patient should be hospitalized and continuous sleep induced. This treatment consists of the administration of a sedative drug in adjusted doses so that sleep is neither too light nor too deep and twenty hours of sleep a day are procured for a period of seven to ten days. During this time the patient receives three to four meals a day. To patients with a more chronic condition a modified form of insulin therapy should be given in a base hospital. By this treatment the patient is rapidly restored to some degree of working capacity, although he rarely can return to the full stresses that precipitated his illness. Convulsion therapy is recommended for the patient with a good previous personality and a genuine, severe depression. This treatment produces rapid improvement in about 75 per cent of patients. Sargant stresses the importance of the use of physical treatment in conjunction with other established methods, both psychotherapeutic and environmental, for patients with acute war neuroses.

ECHOLS, New Orleans.

EPIDURAL CONTRAST INVESTIGATION OF LUMBOSACRAL CANAL IN PROLAPSE OF THE DISK.
F. KNUTSSON, Acta radiol. **22**:694 (Dec. 3) 1941.

In about 20 cases in which clinical signs suggested protrusion of a vertebral disk,
Knutsson carried out roentgenologic studies with epidural injection of perabrodil (same as
skiadon). Ten cubic centimeters of a 1 per cent solution of procaine hydrochloride is
injected and is followed by 20 cc. of 35 per cent perabrodil. A protrusion big enough to
cause occlusion of the epidural space, with complete obstruction, or a protrusion occupying
the greater part of the cross section and thus causing a defect in the contrast shadow can
be discovered. Smaller protrusions may not be discovered.   J. A. M. A.

man in his prime, the possibility of beginning dementia paralytica is always to be borne in mind. On the diagnosis of such a condition, malaria treatment is called for as soon as possible, as the duration of the favorable period for treatment is a matter of weeks, rather than months. Malaria treatment is regarded as the most effective therapy of dementia paralytica. The author reports 4 cases in which such therapy was used.   J. A. M. A.

TREATMENT OF CEREBROSPINAL SYPHILIS. E. LOMHOLT, Ugesk. f. læger **103**:1423 (Nov. 6) 1941.

Lomholt's view is that all forms of recent syphilis in the primary-secondary stage should be given powerful intermittent combined antisyphilitic and malaria treatment. In cases of acute syphilitic meningitis the reaction to the treatment is excellent, and the changes in the spinal fluid in the secondary stage usually quickly yield to the therapy. Until proof is available that powerful antisyphilitic treatment can prevent the later occurrence of neurosyphilis, the author considers this hypothesis as correct. To date, the few small series of cases in which therapy was adequate seem to confirm the hypothesis, he says, and practically all syphilologists of consequence agree that dementia paralytica or tabes is rarely seen in a patient who has had a fully effective treatment of syphilis according to the present day standard. For latent syphilis, with changes in the spinal fluid, in which the age of the infection is often unknown, he recommends immediate malaria treatment. To what extent such therapy can prevent the occurrence of tabes and paralysis is not certain, because no materials have been observed sufficiently long, but he has not seen any case of tabes or dementia paralytica after malaria treatment of syphilis in the latent stage.   J. A. M. A.

Experimental Pathology

SPINAL INJURIES IN SHOCK AND EPILEPTIC CONVULSIONS. JOSEPH E. BARRETT, JAMES B. FUNKHOUSER and W. ALLEN BARKER, Am. J. Psychiat. **99**:387 (Nov.) 1942.

Barrett, Funkhouser and Barker studied four groups of 20 patients each, consisting of controls who did not have induced convulsions, metrazol-treated patients, electric shock–treated patients and epileptic patients. A flat lateral roentgenogram was made of the dorsal portion of the spine of each patient. No fractures occurred in the control group. A total of 5 fractures of the dorsal vertebrae occurred in the electric shock–treated group, 20 in the metrazol-treated group and 17 in the group of epileptic patients. The authors concluded that the fractures in the last group were indistinguishable in type and location from the fractures of the vertebrae in shock-treated patients.   FORSTER, Philadelphia.

Encephalography, Ventriculography, Roentgenography

THE LOCALIZING VALUE OF THE CLINICAL, ELECTROENCEPHALOGRAPHIC, AND PNEUMOENCEPHALOGRAPHIC FINDINGS IN EPILEPSY. HENDRIKUS SJAARDEMA and MARK ALBERT GLASER, Am. J. M. Sc. **204**:703 (Nov.) 1942.

Sjaardema and Glaser compare the relative values of the clinical study, the electroencephalogram and the pneumoencephalogram for the localization of focal cerebral lesions in convulsive disorders in 52 patients. Twenty-four (46.2 per cent) were classified as having idiopathic epilepsy. Twenty-eight patients (53.8 per cent) of the entire series had symptomatic epilepsy. Of the entire group of 52 patients, 32 (61.5 per cent) had electroencephalographic seizure patterns. Sixteen patients showed differences in the alpha rhythms in the two occipital areas. In 33 patients delta and seizure waves originated in a circumscribed area of the brain. For 8 patients, or 15.4 per cent, the pneumoencephalogram was normal, while for 44 (84.6 per cent) some abnormality was noted. Ventricular shift was present in each of 9 patients (17.3 per cent). In all 9 patients the electroencephalogram accurately localized the side of the lesion. Of the series, the electroencephalogram localized the lesion in 33 patients (63.3 per cent), the clinical findings in 31 patients (59.3 per cent) and the air studies in 9 patients (17.2 per cent).

In 10 of the 31 patients with clinical focal epilepsy, the electroencephalogram and the clinical signs localized the lesion in the same lobe. In 7 of these 10 patients the pneumoencephalogram also localized the lesion in the same lobe. Of 24 patients with idiopathic epilepsy, the pneumoencephalogram revealed unequal ventricles in 16. In 6 patients (88 per cent) both the electroencephalogram and the clinical findings accurately localized the lesion. MICHAELS, Boston.

East have told me, and I think Major Ascroft will agree, that if the unit can take only one, it is preferable to have the suction apparatus, for with it the blood clots on the brain caused by the missile can be removed.

Major Ascroft has achieved results in the treatment of gunshot wounds of the brain that have surpassed anything before attained. His treatment of abscess was striking. He did not discuss that; I wish he had. His recovery rate of 75 per cent is much higher than the usual rate of 50 per cent.

DR. GILBERT HORRAX: I shall not discuss this paper, but I wish to thank Major Ascroft and Mr. Jefferson for coming to Boston to speak before this society on subjects in which we as neurosurgeons are so much interested.

I could not but contrast the situations as they pertain to the desert and those in Flanders in World War I. I am sure, as Dr. Faulkner stated, that the strong suction apparatus is one of the chief factors in the reduction of the mortality rate for gunshot wounds of the brain in this war. Obviously, sulfonamide compounds have played a part too, and I wish Major Ascroft had said how he used these — whether systemically or locally. All measures, however—suction, diathermy and sulfonamide compounds—as well as the terrain, must have been factors. The desert is relatively clean and exposed to the sunlight a great deal of the time, whereas in Flanders the field was a sea of mud. Men would fall and come in with their wounds oozing with mud.

Twenty-five years ago it was found that wounds cared for at the base hospital did worse than those cared for in forward areas. just because there were no sulfonamide drugs and adequate suction was not available. Surgeons did learn that it was extremely important to remove fragments of bone and other debris, rather than the metal foreign bodies themselves.

Major Ascroft has given a most interesting paper.

DR. DONALD MUNRO: Something should be said from the point of view of the scientific worth of this paper. Only those who have to do with problems of compound fracture of the skull can appreciate what a low mortality rate Major Ascroft has presented as a result of the treatment carried out by him and his co-workers. The mortality rate of 9 per cent following major compound fracture of the skull, even if the fracture is not complicated by fragments of missiles in the brain, is unknown in civilian practice, at least in this country. It is worth one's while to take notice of this method and to consider seriously its incorporation in private practice.

There were two points in the paper in which I was interested: First, Major Ascroft felt it necessary to comment on a case in which the man died of dehydration. It has long been my experience, also, that the greatest therapeutic need in cases of compound fracture of the skull is the administration of fluids shortly after receipt of the wound. This has proved to be our most usual advice in New England. I am delighted to have Major Ascroft's experience confirm ours. Second, in modern brain surgery under war conditions irrigation in treatment of compound fracture of the skull has been eliminated. This seems to me to be an extremely important factor and one of which surgeons in civilian practice should take note. It has indeed been a great privilege to hear the report of this extraordinary experience.

DR. WILLIAM J. MIXTER: I should like to add my word of thanks to Major Ascroft, as well as to Mr. Jefferson. We of this society are privileged in getting this information, and I am sure it will be of great value to surgeons of this country in the handling of such casualties. We owe our thanks not only to these men but to the British government, which allowed them to come.

MAJOR PETER ASCROFT, Royal Air Medical Corps: Professor Jefferson and I have looked forward to this trip ever since we heard that there might be an opportunity to come, and we shall always remember it with the greatest pleasure.

Work of the kind I have described is essentially team work, and I know the members of my unit will be extremely gratified when they hear the complimentary things that have been said about their methods in this country.

First, I must say that there is no collusion between Dr. Faulkner and myself. His comments were entirely spontaneous. I agree with him that the suction apparatus is the most important factor in the surgical treatment of head injuries.

Dr. Horrax asked about the use of sulfonamide compounds. For general administration, especially in cases of threatened meningitis, sulfadiazine is the most effective. Our policy was to give it in large doses. If the patient had any difficulty in swallowing or was very ill, so that his absorption was impaired, or if the spinal tract was impaired, we gave it intravenously in doses sufficient to produce a concentration of 15 mg. per hundred cubic centimeters of spinal fluid within twenty-four hours after development of the infection. For meningitis we gave enough to obtain a concentration of 15 mg. in twenty-four hours. We had some cases of meningitis due to the staphylococcus, and the patients recovered with that treatment. For local application we used sulfathiazole almost exclusively. That sounds like bad therapy to some people, for it is well known that application of sulfathiazole to the brain may cause fits. If the drug is spread around liberally after removal of a tumor, it will go into solution rapidly, as the spaces are wide open. On the other hand, in a gunshot wound the subarachnoid spaces are sealed off and the drug does not get into the cerebrospinal fluid in any considerable concentration, at least not in one of more than 3 or 4 mg. per hundred cubic centimeters. We observe one precaution: We never introduce the drug into a wound which communicates with a ventricle. There was infection in 6 of the 150 cases studied.

The suction apparatus, I am sure, has made a tremendous difference in our results. It provides the easiest method of cleaning out a wound of the brain and the simplest way of exposing and removing the little bits of bone which are so dangerous. The introduction of mechanical suction has to a great extent done away with the need for irrigation. The latter measure can be harmful in many cases, especially if a wound is open, for it is easy to blow dirt into the tract of the wound. We avoided irrigation of deep wounds.

Dr. Munro mentioned that the mortality in this series of cases of compound fracture of the skull was lower than that seen in civilian practice. This result is due not so much to us as to the difference in the type of wound. The average wound that occurs in peacetime is associated with a severe concussion effect. The usual injury due to a missile is local and much less severe, with less shaking up of the cerebral tissue.

Care of Head Injuries on a Large Scale. PROF. GEOFFREY JEFFERSON, Manchester, England.

Head injuries occurring both in the military and in the civilian population in Britain have been largely in the care of the special head centers created as an emergency measure for war purposes by the Ministry

Society Transactions

William G. Lennox, M.D., *Presiding*

Regular Meeting, May 18, 1943

Neurosurgical Experience in Egypt and Libya. Major Peter B. Ascroft, Royal Air Medical Corps.

The methods of treatment of missile wounds of the head have been gradually evolved as the result of nearly two years' experience in the Middle East. In a war of movement segregation of different types of cases is impossible in forward areas. At the base, when casualties are heavy, specialized units cannot hope to deal with more than a fraction of the cases. The military surgeon must be prepared to deal with wounds of all kinds. The functions of specialized units should be to deal with particularly difficult cases, to study intensively special kinds of injury and to make their results known.

The accompanying table shows the fate of 516 patients wounded in battle by missiles who came under the care

The general principles of treatment of all wounds, chief of which is early excision for prevention of sepsis, apply to injuries of the head no less than to wounds of other parts. There are, however, certain peculiarities of structure and function of the brain and its coverings which influence the behavior of head wounds and their treatment.

1. The scalp is richly supplied with blood; it has considerable resistance to infection and heals well.

2. Spreading osteomyelitis of the skull is rare (there was no instance in this series of more than 400 men with compound fracture).

3. The intact dura is a powerful barrier to the spread of infection, and the meninges as a whole have considerable power to localize infection.

4. The tissue of the brain resists infection well, provided the products of trauma and inflammation are not allowed to accumulate under pressure.

5. Continued exposure of the brain in an open wound is always harmful and is always associated with some degree of infection. It follows that some delay before

Data on Severity of Injury, Mortality Rate and Disposal of Men with Head Wounds

Severity of Injury	Mortality for Whole Series			Disposal of Recovered Patients *			
	Number of Patients	Number of Deaths	Mortality, Percentage	Number of Patients	Men Invalided on Account of Head Wound †	Men Returned to Duty	
						Number	Percentage
Scalp wound only	85	0	0	80	1	76	95
Fracture of skull, dura intact	139	2	1.5	130	10	110	85
Dura pierced	292	44	15	226	93	124	55
Total	516	46	9	436	104	310	71

* Data were not available for 34 patients.
† Twenty-two patients whose head wounds did not incapacitate them for duty were unfit because of other wounds.

of a mobile neurosurgical unit attached to a general hospital at the base. Patients arrived at intervals of from a few hours to more than a week after injury. About three fifths of the men had undergone operation while in forward areas; one-fourth underwent primary operation after reaching the base, and one-eighth were not operated on at all. All patients were kept under observation until they were fit for duty or, if unfit, until they were well enough to be evacuated from the command (seldom less than sixty days after injury). The unit worked for a time in forward areas, thus gaining first hand experience with battle casualties within a few hours of injury and under the somewhat difficult conditions prevailing in the open desert near the fighting zone.

Head wounds which are not immediately fatal are less lethal and crippling than is popularly believed (table). The proportion of men who returned to duty, even after severe penetrating injuries, was much higher than was anticipated.

The great lesson of this war is that treatment of battle casualties depends as much on local conditions as on the nature of the wound. Today a fixed line of battle is the exception—conditions vary from day to day, and even from hour to hour—and the physician, no less than the fighting man, must be prepared without notice to alter his orthodox plan of campaign.

operation is less harmful than might be supposed from experience with wounds elsewhere, since sepsis is seldom established soon, and that closure of the wound is highly desirable as a means of protection of the exposed brain and is often successful in acceleration of healing.

6. Organic damage to the brain is irreparable, and even the gentlest surgical manipulations are damaging in some degree.

7. Surgical manipulations within the skull cannot be carried out effectively without preliminary roentgenograms and special apparatus, especially an efficient mechanical sucker.

8. "Every scalp wound, no matter how trifling, is a potential penetrating wound of the skull" (Cushing, 1918).

DISCUSSION

Dr. J. M. Faulkner: Major Ascroft has reported the experience of the Eighth Army with regard to head injuries and has given conclusive evidence that it is preferable to wait until the men can be taken back where the proper facilities for treatment are available. He did not state what those facilities are. There are two: first a suction machine and, second, an apparatus for diathermy. The mobile unit to which I was attached had both, and they enabled Major Ascroft to get the results he did. Others who have been in the Middle

for peripheral nerve injuries. This is a tremendous step in treatment; there is not that system here.

I should like to express my appreciation of this excellent paper.

PHILADELPHIA NEUROLOGICAL SOCIETY

GEORGE D. GAMMON, M.D., *Presiding*

Regular Meeting, May 28, 1943

Spinal Shock. DR. GRAYSON P. McCOUCH, DR. JOSEPH HUGHES and DR. WINIFRED B. STEWART.

Spinal shock was defined as the more or less transient depression of reflexes following partial or complete transection of the neuraxis. After a brief survey of early inhibitory and circulatory theories of its production, the work of Sherrington, which replaced them with the concept of loss of facilitation from descending tracts, was reviewed in some detail, with passing reference to more recent work attempting to allocate the influence of vestibulospinal and corticospinal pathways. Van Harreveld's experiments with ischemia and the theory of inhibition which he evolved from them were briefly discussed.

The results of synchronous recording of intermediary cord potentials and reflexes concerned with the degree of block at interneurons and at motoneurons in different species were reviewed.

DISCUSSION

DR. HENRY WYCIS: I should like to discuss two points: First, Trendelenberg passed a small tube around the upper part of the spinal cord, through which he circulated ice water. He showed that the responses were reversible if the ice water was replaced with warm water. Second, Munk, in his classic experiments, studied two sets of dogs, both with transverse sections of the cord. One set he left entirely alone, while the other set he exercised, stimulated and examined daily. The dogs which were exercised showed a rapid return of spasticity, increased reflexes and hyperactivity, while the dogs which were not stimulated or exercised showed a return of spasticity, but only of a mild nature and after a prolonged period. He expressed the opinion that the lower motor neuron, being isolated from the influence of the higher centers, acquired a state of hyperexcitability and that this state was increased by afferent impulses. Perhaps these experiments of Munk help to explain some of the problems concerned with the bladder that arise after injections into the spinal cord.

DR. GRAYSON P. McCOUCH: Without question, cerebral injury resulting in loss of reflexes should be classified as spinal shock. It is at the spinal level that withdrawal of facilitation from above produces its effect. The reason the effect does not last as long as that with transection of the cord is that a smaller fraction of the ascending pathways are cut off.

With regard to flaccidity versus spasticity, I can add little except a word as to the reason for the reflex picture. The degree of depression of each reflex is presumably determined by the percentage of its central drive removed by transection. After corticospinal lesions, reflex movements of the hand and foot suffer more than those of proximal segments of the limbs, for the same reason that loss of voluntary control follows a similar pattern—the heavy representation of digital movement in the motor cortex. Consequently,

if after recovery of reflexes lost by ablation of area 4 the cord is transected, movement can be elicited earlier on the previously paretic side and the asymmetry will be greatest in the movements which suffered most from the cortical ablation. Since the monkey is an arboreal animal, the movements of grasping are highly developed on a purely spinal basis. Hence, in that animal they form the focal point of recovery after transection. Since the major site of shock in the monkey is in the anterior horn, crossed reflexes, like the ipsilateral ones, return first on the side of earliest recovery and in the units which respond most readily to ipsilateral stimuli. Thus, digital flexion, which is the first ipsilateral reflex, is likewise the first crossed response, and only after a week or more is it gradually replaced by crossed extension of the entire limb. One is tempted to speculate that the paralysis in extension, characteristic of incomplete transection, may be due to a less vulnerable position of the vestibulospinal tract than of the corticospinal path. It would be interesting to know whether a completely spinal man may not ultimately pass from a reflex balance yielding crossed flexion to one which favors crossed extension, the course following in terms of years that run by the monkey in a period of weeks or days and by the cat in one of hours or minutes.

With regard to the bladder: In the monkey, as in other laboratory animals, an automatic bladder may be established—in fact, more readily in the monkey than in the cat. I believe this is because the external sphincter muscle is less of an obstacle in the monkey than in the cat. What produces the dilated bladder, with no tone to speak of? I believe it may be explained by the presence of one, and only one, mechanism for inhibition of the external sphincter, that mechanism being the development of a strong stretch reflex in the detrusor muscle of the bladder. The bladder suffers from spinal shock; its stretch reflex is depressed, and consequently the external sphincter stays tight shut.

Laboratory animals recover to the point at which the bladder contracts again and expels urine in jets, with the clamping down of the sphincter and the resultant periodic interruption of micturition.

Analysis of Convulsive Movements by Slow Motion Pictures. DR. TEMPLE FAY.

The constant pattern of flexor-extensor movements seen in a major convulsive seizure following electric shock was analyzed synchronously in colored moving pictures at normal and at slow rates of speed. These characteristic movements strongly suggest swimming movements in a primitive amphibian pattern. When infants are placed on the abdomen, the flexor-extensor pattern is that of a swimming movement. Activities of the fish, tadpole, salamander, guinea pig and rat as they respond in a fluid environment were shown in slow motion picture. The same pattern of movement is exhibited by the fish, frog and salamander as that presented by the guinea pig, the rat and the human infant when placed on the abdomen and suspended under water so that free swimming activity can be noted. A special apparatus was devised to immerse rats and guinea pigs so that swimming movements could be noted with the animal in the normal swimming position after administration of doses of convulsive drugs sufficient to produce seizures. The observation indicated that the convulsive seizure is a release of a primitive amphibian swimming pattern rather than the result of cortical stimulation or irritation. It was suggested that the movements seen in a major convulsive seizure are in reality reactions of defense manifesting

of Health. This arrangement has on the whole proved satisfactory once the persons in charge realized the special aims of the services. It has permitted the British to be economical of their highly trained and specialized staffs, always too few in any country to allow of lavish provision for the fighting forces as well as for the essential workers in airplane and munition factories and for the families of the soldiers themselves. In ordinary civilian life concentration is all on the immediate, acute period; patients remain hospitalized for two or three weeks and travel the further steps of recuperation in home surroundings. Too often they build up exaggerated notions of the seriousness of a head injury and of their own injuries. Follow-up studies as a rule are made for scientific purposes and are best carried out as late as possible, for the determination of end results. Military considerations and the need to conserve manpower in factories have changed this objective. The large number of new beds available in Britain has made it possible for hospitals to retain patients longer than was the custom, and the patients have been carried through stages of rehabilitation under the direction of the clinician. Follow-up observations have been immediate, and contact with the patient has been maintained through the social worker (or Red Cross worker) or through regimental or other service medical officers. My colleagues and I have found it best to get the patients up early and not to permit their discharge until they feel well. This has led to the discovery that in the main they recover quickly, much more so than is commonly assumed and taught. I suspect that the good results which the advocates of routine dehydration have reported in their follow-up studies have gained overmuch credit because they have not been offset by the results of other treatment. Most surgeons, using more conservative methods, have not inquired how their patients have done. It is one of the curiosities of medicine that whenever surgeons gather to discuss head injuries they tend to fall into argument over the worst cases. They forget that the great majority of head injuries are mild; they would arrive at a more balanced judgment if they spent more time thinking about the lesser wounds as well. Furthermore, the surgeon's and the neuropsychiatrist's most vivid recollections of head injuries derive from the high grade neurotic patient and the litiginous patient. It is small wonder that the impression is deep, for these persons are powerful advocates of their subjective complaints. The mortality from bomb wounds of the head varied from 2.5 to 8 per cent, and the over-all mortality rate for persons with closed injuries to the head admitted to the special neurosurgical centers in Britain was about 5 per cent. The latter figure not only indicates that the treatment has been good; it is due particularly to the inclusion of relatively minor injuries which were cared for, as well as severe wounds. This factor has acted as a diluent to reduce the mortality, but its recognition gives a better idea of the real problem of head injuries. Patients are got out of bed as soon as they can sit up without discomfort, a point that may be reached in three or four days. We have abandoned the plan of keeping the patient flat; we treat him with the head high. We have also abandoned the rule of thumb practice of keeping the patient flat or bedfast for two, or even three, weeks. The results of the change have been revelatory. It is necessary to know whether cerebral laceration is present; so in all cases puncture is made as a diagnostic (not as a therapeutic) measure at some time during the first or the second day. In my own clinic, Dr. Bailley has been making differential punctures, cisternal and lumbar, and has found that the red cell count of the cisternal fluid is usually as high as, or higher than, that of the lumbar fluid. This seems to rule out sedimentation as the cause of the heavy staining of the lumbar fluid with blood which is sometimes seen. It is my belief that most of the blood in the spinal fluid comes from vessels that have easy access to the basal cisterns and that it is more often arterial than venous. Venous hemorrhage tends to be subdural rather than subarachnoid, though, to be sure, subdural bleeding may well have an arterial source, as all have seen.

Treatment in these centers has been conservative; in only one or two centers has dehydration been practiced. The post-traumatic syndrome is always neurotic when no blood is found in the cerebrospinal fluid. Even when blood is present, the patient is generally free from symptoms if he is kept from the contaminating influence of relatives, friends and neighbors. The neurosurgeon is accustomed to inflict severe, if locally controlled, injuries on the human brain, and nowadays he is not surprised if the patient is able to return to work without complaint, or in spite of mild complaints. Yet by some queer twist of reasoning, if a patient has sustained much less damage from a blow on the head, he is held entitled to compensation for disabilities. The key to many difficulties is the use of the psychiatrist, not as a therapeutic agent but as a diagnostic colleague. In England, a close association is springing up between the neurosurgeon and the psychiatrist which bids fair to be a fruitful partnership. In rehabilitation the chief emphasis should be on the entertainment of the patient's mind, rather than on the physics of his limbs. He must live according to a time table and be kept interested by some sort of occupation. Physical therapy, electric stimulation and diathermy are relatively unimportant adjuncts to treatment and must be kept in their proper place. The man must be treated as a thinking organism, not as an integrated nerve-muscle preparation. Above all, he must be prevented, as far as possible, from the very human failing of wishing to increase his self importance and self esteem by building up an idea of himself as one who has been through great danger and is lucky to be alive. I see the danger of not understanding real disability, but a carefully conducted program of rehabilitation that utilizes psychologic tests, weighs past performance and judges character should prevent grave injustice.

DISCUSSION

DR. JAMES C. WHITE: Two years ago it was my privilege to be sent by the United States Navy to England, after the heavy bombings, to see what was being done about head injuries. It was Mr. Jefferson who showed me the work he was doing and then came to London to point out to Dr. Penfield and me the things we should see.

I was impressed by the fact that men like Major Ascroft and Mr. William Henderson were sent to Egypt and that the men on the home front were organized so that they could look after the needs of the army, navy, air force and civilians. One man could do a tremendous amount of work in that way, and more economically than by having as here, for example, a neurosurgeon at Camp Devens, another at Camp Edwards and another here in Boston. In England one man would do all that work, and great benefit would be obtained from such experience.

In England there was a system of regional hospitals; for example, at Oxford there was a special center for men with head injuries, and there were other centers

Book Reviews

Behavior and Neurosis. By Jules H. Masserman, M.D. Price, $3. Pp. 269. Chicago: University of Chicago Press, 1943.

The author's aim is to describe a series of experimental studies of animal behavior, in the belief that these studies contribute materially to the understanding of human behavior. He indicates the applicability of basic psychobiologic principles to psychoanalysis, clinical psychiatry and psychotherapy. The volume is divided into three parts: part 1, historical rationale and experimental results; part 2, a survey of relevant literature on dynamic psychology and experimental neurosis, and part 3, an introduction to the clinical applications of the data recorded.

The experimental data were acquired by a study of cats in a glass-enclosed cage equipped to provide incentives to behavior under controlled physical, spatial and temporal conditions. The cage was also equipped to provide sensory stimuli, and likewise it included means of frustrating adaptive behavior or of making the behavior conflictual. The incentive used was food served into the cage in cups mounted on a rotary wheel which opened into a feed box in the cage. The animal could get to the food by lifting the door of the feed box. Conflict-producing situations were produced by a blast of air from a fan directly across from a feed box, or by electrical shocks to the metal grill floor of the cage or to a smaller, movable escape platform. Bell, light and buzzer signals were provided.

In the first chapter the author formulates the following cardinal dynamic principles, derived from psychoanalysis: (1) Behavior is fundamentally motivated by needs of the organism; (2) behavior is related to an inner apperception of a total field situation, i. e., is imbued with a configuration of meaning to the percipient; (3) behavior is not always a simple and direct fulfilment of elementary needs, and (4) motivation may become conflictual because of the necessity of difficult adjustments to symbol. Masserman feels that the extension of these principles into the fields of general and comparative psychology has been neglected by psychoanalysis.

He then formulates these dynamic principles of behavior in psychobiologic terms as follows: (1) Behavior is fundamentally motivated by psychologic requirements of the organism; (2) the adaptive nature of behavior is related to the significance of the situation to the percipient; (3) behavior under partial frustration may take the form of symbolic expression and substitutive satisfactions, and (4) when meanings of the perceptive fields become confused or conflictual, behavior becomes inefficient, inappropriate, excessively symbolic and substitutive.

The author devotes a chapter to controverting effectively the recent tendency to undue stress on the role of the hypothalamus in the connotive and expressive aspects of behavior. He feels that one should assign to the hypothalamus its experimentally demonstrable role in reenforcing and coordinating the neural and hormonal mechanisms of connotive and emotional expression and reserve for more adequate proof the hypothesis that it is either the dynamic source or the seat of experience or affective states.

He then develops the thesis that "conditioned behavior" (i. e., adaptive response to significant symbols) can occur only in the experimental animal if the stimulus situation is made meaningful to the animal. "Behavioral" response should then become "neurotic" in character if the motivational connotations are made conflictual to a sufficient degree. This is in contrast to emotional-mimetic responses, such as sham rage, which are obtained by hypothalamic stimulation when there is no motivational connotation or meaning, and can therefore neither be conditioned nor made the basis for an experimental neurosis.

The author then proceeds to describe the training of cats to lift the lid of the box and procure food at a sound or a light signal. At first, frustrational effects caused by locking the box, etc., were produced, but no "neurotic" behavior developed. Then conflictual effects were produced by subjecting the cats to air blasts and/or electric grid shocks, and there developed in the animals an experimental neurosis characterized by a number of neurotic symptoms, such as chronic anxiety, phobic responses and compulsive behavior. The author was able to treat these experimental neuroses by such "therapeutic" technics as rest, diminution of intensity of the conflictual hunger drive and reassurance.

Part 2 of the book is a critical review of the experimental studies of behavior and of the neuroses. Part 3 develops the clinical and psychotherapeutic applications of the foregoing material. It should be noted that in this book of 269 pages of reading matter, only 12 pages are devoted to this portion, and they consist essentially of a restatement of the therapeutic technics developed in previous chapters of the book. In this connection the following statement is of interest: ". . . there are paramount differences between animal and human behavior which must be recognized in every discussion of the subject, . . . a cat has within its repertoire only a few and relatively primitive patterns even of normal behavior: its 'neurosis' can consist therefore only of correspondingly simple deviations. Although the patterns of these phenomena are highly suggestive of their persistent and elaborately symbolic counterparts in the human, nevertheless, no cat that I have observed has thus far had the

a primitive attempt to readjust the mechanism to the free swimming state when normal relations in oxygen, water and salt become available. It is noted that these convulsive movements appear in forms above the amphibian level which have emerged from the free swimming state. A fit may be considered from the standpoint of its normal polygenetic origin rather than from the superstitious position of an evil disease or spirit. A fit may be a normal release phenomenon of a motor pattern at the amphibian level when higher cortical control centers are obliterated or temporarily removed.

DISCUSSION

DR. D. J. McCARTHY: I have little to add to what Dr. Fay has said. He stated that years ago the possibility of the epileptic attacks being a mass reflex phenomenon was suggested. The goldfish out of water, attempting to get back, may be exhibiting the effects of anoxemia of the cerebrum. The immediate cessation of the movements when it gets back into the water supports this view. It is unreasonable to assume that the fish thinks out these movements; they must be a protective reflex mechanism. Every one knows that a child swims before he walks. These pictures have shown that the typical epileptic convulsion consists of full flexion and extension movements. In the electrically induced convulsion rotary movements follow the anatomic structure of the cortex. This presentation has been extremely stimulating; furthermore, any one who thinks about epilepsy deserves encouragement.

DR. TEMPLE FAY: These moving pictures show that skilled movements and the acquired, educated movements in the human subject were absent. It is important to bear in mind that the type of movement in a convulsive seizure observed in an infant 2 days old is similar to that manifested by an adult, after years of motor training and specialized movements attributable to the motor cortex.

I agree that a full-fledged convulsion must be mediated through the motor cortex. However, I believe that the neurophysiologist should try to get away from the idea that the convulsion arises in the motor cortex. The convulsive seizure seems to me a spontaneous pattern manifested when a certain amount of cortical influence has been withdrawn. It is therefore, in my opinion, not a stimulation but a release phenomenon.

I differ with Dr. McCouch in the emphasis he places on the motor cortex in the convulsive attacks. One can get representative convulsions from the midbrain after the cortex has been removed. In fact, even when the cerebral peduncles have been sectioned, a form of "spinal epilepsy" arises which in pattern is not far removed from that observed in the full-blown attack. One should encourage the idea that the fit is a normal release phenomenon rather than foster the old concept that the cortex is the place of origin of the convulsion.

The Techniques of Self-Help in Psychiatric After-Care. Developed by Recovery, Inc., the Association of Former Patients. By Abraham A. Low, M.D. Vol. I. Recovery's Self-Help Techniques: History and Description. Price, $1.25. Pp. 138. Vol. II. Group Psychotherapy. · Price, $1.25. Pp. 88. Vol. III. Lectures to Relatives of Former Patients. Price, $1.25. Pp. 125. Chicago: Recovery, Inc., 1943.

These three books, sponsored by the Association of Former Mental Patients, give a comprehensive report of an imposing system of group technics evolved by the author. Dr. Low is the founder and president of the association and is associate psychiatrist at the Neuropsychiatric Institute of the University of Illinois.

The first volume consists of articles and items previously published in the bulletin of the association, and deals with the historical development of the association from the time of its foundation, in 1937, to 1943. The aim of the association has been to eradicate the stigma attached to mental disease, through various activities in the social, economic and legal spheres, directed and executed by the members themselves. These measures have included, in addition to social activities among its members, publication of a bulletin, to which members are encouraged to contribute, arrangement of public lectures and radio talks to enlist support for revision of the commitment laws of Illinois and operation of a labor exchange to find employment for former patients.

The second volume, as its subtitle indicates, is "a record of class interviews given to patients suffering from mental and nervous ailments." It consists of twelve interviews, divided into three parts. The first eleven are of the "single interview" type, in which the symptoms of one patient are discussed by the therapeutist in the presence of other patients. The twelfth is of the "multiple interview" type, in which the symptoms of one patient are discussed by several other patients under the guidance of the therapeutist. The method used by the author contains much of the repressive-inspirational factor, with little of the analytic. Intellectualization, that is, understanding and mastering the symptoms, and Dubois' technic of persuasion therapy are stressed. The first part of the book contains three interviews, which deal with topics of sensation under the headings: "Real Sensations and Fantastic Interpretations"; "Normal and Abnormal Interpretations," and "Sensations are Distressing but Not Dangerous." The second part contains eight interviews, in which are discussed various symptoms and mechanisms, such as "the vicious cycle of panic" and "adult versus infantile valuations." In the third part more difficult material, such as "intellectual versus emotional insight" and "will training and tenseness," is discussed. Throughout the book generous use is made of contrast formulations, as shown by the titles of the interviews cited.

The third volume consists of fifteen lectures selected from a series given by the author twice a month during a three-year period before an audience composed of relatives of patients of the Neuropsychiatric Institute of the University of Illinois. In the introduction, Low discusses the importance of the "domestic scene" to which the patient returns from the hospital, and which is often responsible for his relapse. The role of overprotection, which the patient resents, often leads to temperamental explosions. The first six lectures deal with general principles of constitution and environment and with standards of behavior, such as moral, legal, ethical, esthetic and conditional; the importance of the domestic trivia of everyday behavior is stressed. The author then discusses motives of behavior and classifies them as those of service and those of domination, types which give rise respectively to submissive and domineering dispositions or temperaments. The remaining lectures are devoted to temperamental deadlocks and their control. Insight and understanding of the working mechanism of temper, plus persistent practice in control of temper, are suggested as therapeutic means. In this book the author continues with contrast formulations, such as inclinations versus obligations, emotional balance versus intellectual instability and will to peace versus will to power.

In the opinion of the reviewer, the three books offer interesting material on another approach to the broad problem of psychiatric after-care of discharged patients.

Contemporary Psychopathology. Edited by Silvan S. Tompkins. Price, $5. Pp. 600, with index. Cambridge, Mass.: Harvard University Press, 1943.

The subtitle to this volume describes it as a source book, and the preface states that it is designed for courses in abnormal psychology. While the editor has thus defined the limitations within which he has chosen the material, it seems best for the purposes of this review to consider the book mainly from the point of view of its title, i. e., contemporary psychopathology, without the additional limitation described.

The volume is a collection of 45 papers gathered together from widely distributed current scientific periodical literature. That this material can be considered truly current is indicated by the fact that only 8 articles were published prior to 1939 and only 1 prior to 1933. The book is subdivided into four sections, as follows: (1) mental diseases in children; (2) psychoneuroses and psychosomatic medicine; (3) the schizophrenic psychoses, and (4) experimental psychopathology.

The first section, on mental diseases in children, consists of 7 articles and concerns itself with dynamic interpretative material on the developmental problems of infancy and childhood. No space is devoted to a discussion of psychoses in children, delinquency problems or other material which might be considered important to workers in this field.

In the second section, devoted to the psychoneuroses and psychosomatic medicine, there are 10 articles, 4 of which are concerned with the important consideration of the gastrointestinal tract as the seat of expression for psychosomatic disorders and 1 each with the respiratory and the cardiovascular system as the site of dysfunction. The remaining articles are given over to methods of investigation and treatment of some psychoneurotic disorders, including war neuroses. In this section one might ask for additional material on such disorders as arthritis and migraine.

The section on the schizophrenic psychoses consists of 13 articles, in which schizophrenia and schizophrenic processes are surveyed from the physiologic, the psychologic and the psychodynamic point of view. The articles on therapy cover insulin and metrazol shock, prefrontal lobotomy and modified and specialized analytic technics. The absence of material on electric shock is apparent.

The last section, devoted to experimental psychopathology, covers, as it must, a wide variety of subjects, including data on animal, as well as human, material. Frustration experiments, conditioned reflex studies, hypnotism, stress studies and topologic and vector psychology are discussed. One might ask for a more extended consideration of the use of thematic apperception technics in the study of the neuroses and psychoses.

imagery to solve its anxiety by strutting, growling, or dressing like Mussolini in over reaction to feline feelings of frustration and inferiority."

In the introduction to the third part the author states that the previous sections have been devoted to a demonstration of the psychobiologic principles underlying the phenomena of "normal" and "abnormal" behavior in general, i. e., in both animals and man. He feels that the task of reviewing the application of these principles to psychiatry, psychoanalysis and clinical psychotherapy should have been reserved for a separate book. With this opinion the reviewer concurs.

Within the limits which he has set, the author has done an excellent job in attempting to integrate comparative psychologic, psychobiologic and psychoanalytic data. It should be remembered constantly that the author's endeavors are directed to explaining behavior and motivational conflicts in a cat, admittedly an animal of much simpler and more elementary modes of reactive adaptability than man. The book is highly recommended as a bold step toward a long-needed and much to be desired integration of what were once considered incompatible scientific doctrines.

The Psychiatric Novels of Oliver Wendell Holmes. Abridgement, Introduction and Annotations by Clarence P. Oberndorf, M.D., Clinical Professor of Psychiatry, Columbia University. Price $3. Pp. 268. New York: Columbia University Press, 1943.

In a recent address before the New York Academy of Medicine, Reginald Fitz said that Holmes was a man a hundred years ahead of his time. This was stated at a meeting celebrating the hundredth anniversary of Holmes's paper on the infectious nature of puerperal fever. In psychiatry he was perhaps not a century ahead of his time, but at least seventy years, for he wrote his three "medicated" novels in the latter part of his life ("Elsie Venner," 1859; "The Guardian Angel," 1867, and "A Mortal Antipathy," 1885). They were unsuccessful and were severely criticized; in fact, "Elsie Venner" is the only one that is a passably good story and has literary merit; the other two seem inept and amateurish as compared with his essays and scientific papers. The reason may be that Holmes was for once indirect and was writing about subjects which he knew would not be understood; as he put it, the subject matter "would have to be wrapped in some tissue of circumstances or would lose half its effectiveness." It has taken three quarters of a century for a commentator to see the merit of Holmes's books. We owe to Oberndorf much gratitude for the discovery and for the scholarly treatment given the subject. His abridgments make the novels more readable; his introduction gives a brilliant picture of Holmes, and his annotations explain to people not trained in psychiatry the importance of the text. To the psychiatrist the text needs little explanation; the clinical descriptions are masterly, and many theories are clearly stated which would now be called "freudian."

"The theme of *Elsie Venner* was a lifelong favorite of the author, namely that there is no such thing as total depravity. Because of his inherited tendencies no man can be held completely responsible for certain traits of character, certain deficiencies, mental quirks, or even criminal inclinations. The will therefore is never completely free. Later Holmes formulated this lack of complete control of our actions as being due to the continuous operation of unconscious impulses and thought."

"*The Guardian Angel* is psychiatrically by far the most significant of Holmes's three novels, as it introduces specifically many factors which are today considered of essential importance in the production of mental disorders. Among these may be mentioned such questions as the pernicious influence of austerity upon a child, the power and effect of unconscious forces, the elements entering into personality formation, and the role of faith and religion as curative agents."

"Particularly unexpected is the fine understanding of the nature of transference, often regarded as an entirely modern contribution, as a guide to the interpretation and treatment of psychiatric reactions. Furthermore, we come upon the concept of regeneration through rebirth, and finally, the rehabilitating and integrating effect of the liberation of repressed love impulses."

"*A Mortal Antipathy* is from a psychiatric standpoint the simplest and most direct of the novels. Perhaps it is oversimplified for it represents Maurice Kirkwood, the sufferer from a phobia, as perfectly normal except in respect to his fear of women due to a single infantile shock. It presents theories far in advance of that time concerning the structure of neuroses and the understanding and management of such cases. One may consider it as a summary of observation and theories with which Holmes had occupied himself over the last three decades of his life."

From the text of the three books, it is clear that Holmes believed in phobia arising from psychic trauma in infancy, in hysteria arising from emotional conflicts in a girl whose instincts (inherited reactions) and ideals were incompatible and in habitual invalidism arising from repressed jealousy, "a feeling which had hardly risen into the region of inwardly articulated thought but lay unshaped beneath all the syllabled trains of sleeping and waking consciousness." He also described projection and used the term in its current psychiatric sense; he spoke of "unconscious dramatization"; he considered it his task "to lay bare all the springs" of his heroine's action, i. e., psychic motivation. There is no doubt that Holmes had remarkable psychologic insight and could have initiated dynamic psychology in 1870 if the medical world had been ready to accept it.

laws of the Universe. Forever and ever are we bound to the earth no matter how far we seem removed. Our clay feet must march to the deadly drum beat of the Cosmic Master, if not, we merely perish the sooner. With age our clay feet tire, and some time we will miss a beat. But the stream of youthful protoplasm will march on while we, who are dust, blow away into the evening."

It must not be supposed that all parts of the book are equally elegiac, but the author, in his interpretations of events in terms of weather and the cosmos, lifts his eyes beyond the usual horizon of the individual and calls on Hippocrates to witness that besides man himself there are airs, waters and places. The book reads well beside a wood fire, with the patter of rain and the sough of the wind outside. Man tends to forget about the weather when, in this machine age, he has finally succeeded in doing something about it.

Neurologia ocular. By E. Adroqué. Pp. 882, plus index. Buenos Aires: El Ateneo, 1942.

This is the best comprehensive treatise on the neurology of the eye since the publication of Wilbrand and Saenger's "Handbuch." It is a magnificent volume, clearly written, obviously on a basis of wide personal experience, and richly illustrated. There are excellent chapters, with clear diagrams, on the coordination of ocular movements and their disturbances. The section on binocular vision is notable for its clarity and its scholarly approach.

The chapters on the pathology of the eye and the optic nerve are exhaustive. They are illustrated with actual photographs of the fundus, which are convincing but not always as clear in detail as drawings. The visual fields which are presented are for the most part from cases in the author's own experience; they are invariably taken with several disks by the Walker technic. Particularly outstanding are the chapters on tumors of the chiasmal region. The medical disorders of the eye are also covered in detail.

The value of the work would have been much enhanced by a bibliography. The presswork is excellent.

Women in Wartime. Price $0.35. No paging. Chicago: Institute for Psychoanalysis, 1943.

"Women in Wartime" is a pamphlet published by the Institute for Psychoanalysis, in Chicago. No authors are named.

An attempt is made to outline some of the emotional adjustments of women in their everyday life in wartime; as the article states, the discussion is directed to people who work with women and must understand their needs. The pamphlet is divided into six chapters, entitled, "Women in Wartime," "Changes in the Family," "Separation," "Women at Work," "Rationing" and "At Home and Abroad."

The material is well organized but contains little that has not been frequently discussed. Taken as a whole, the content seems directed to the laity rather than to the medical profession. Some psychologic interpretations are given, but for the most part they are superficial. One gets the impression that the material is selected for a general audience and that more profound interpretations, which would have been of interest to the psychiatrist, have been omitted.

The criticism may be made that frequently the extremes in reactions are given much prominence, whereas the more common and usual reactions are only mentioned.

The pamphlet can be recommended for a general understanding of some of the emotional reactions in women in wartime, and it is to be hoped that it may stimulate interest in further study.

Development in Adolescence. By Harold E. Jones. Price, $2. Pp. 161. New York: D. Appleton-Century Co., Inc., 1943.

The book is a report based on the record of 1 boy for a period of seven years, from 12 to 17 years of age. The boy is selected from a group of 80 children who were studied by the Adolescent Growth Study Institute of Child Welfare of the University of California. A mass of data about the boy is condensed into this rather brief summary. Instead of a presentation of the usual tables of averages for the group, a careful analysis of this individual and his relationship to his group is presented. The theme is that of a boy with many soicial handicaps and inferiorities who has a tremendous drive to succeed and with his first year at college has outwardly begun to achieve some success. Before his fifteenth year he was undersized but then had a rapid growth to normal stature. With this came a better adjustment. The difficulties the adolescent boy encounters because of physical inaptitude are clearly revealed. A vivid portrayal of the internal conflicts and the boy's attempts at counteracting his own handicaps is presented. The deviation in behavior that may occur within normal limits in adolescents, but with an eventual normal development, is demonstrated. The book is well worth reading. However, no dynamic interpretations are given. Much too little space is devoted to the influence of a demanding, exciting, dominating mother, who ruled not only the child but her husband. Also, the sexual problem of the adolescent boy is not mentioned, except in terms of social dancing.

The reviewer has considered the subdivisions in some detail and has noted possible additional data which might have been included in conformity with his announced intention of discussing the book for the most part from the point of view of its title, "Contemporary Psychopathology, a Source Book." However, as one reads along in this volume, one cannot help but be struck by the tremendously widened horizons of the psychiatric landscape. It becomes apparent how utterly impossible a comprehensive survey of psychopathologic phenomena really is. The material from certain contemporary trends in psychopathology and psychotherapy is chosen. In the words of the introduction, these trends are chiefly three: (1) the spread of psychoanalysis; (2) the emergence of psychosomatic medicine as a new discipline, and (3) the development of experimental procedures, suitable to the investigation of vital problems of human behavior.

With this decision on the part of the editor so to limit his material one can have no quarrel. He is rather to be congratulated on his guiding the reader so straight through the otherwise impenetrable jungle of accumulated psychologic literature. Aside from the obvious merit of this collection for use in courses in abnormal psychology, its place on the reading shelf of the literature-swamped psychologist, psychiatrist and psychoanalyst seems assured. The book is highly recommended.

Mind: Perception and Thought in Their Constructive Aspects. By Paul Schilder, M.D. Price, $5. Pp. xxi, plus 432. New York: Columbia University Press, 1942.

This is an exciting book—stimulating, arresting, irritating at times. It was virtually completed by Schilder before his untimely death, but shows evidence toward its end of slackening in the acuteness of reasoning that is present in the earlier parts. One would have enjoyed further discussion of the nature of consciousness and of psychic energy. As he indicates in his foreword, Schilder uses the principles gained in the investigation of the body image in an attempt to define the phenomena of perception and thought. He continues: "I extend the results and methods of modern psychology into a field which so far has not been studied from this point of view. As is every serious worker in this field, I am deeply influenced by Freud. However, guided by my own efforts and by my own material, I have developed my own ideas. Freud's work is an era in psychology. In order to utilize it fully, new, independent efforts are necessary."

Schilder's style is rather jerky. He advances one striking hypothesis after another, often with an assurance that is scarcely justified by the context, and the foundations for his theories must probably be sought in the teachings of his school of philosophy. Indeed, if this were the first book of the author's encountered, the reader would be confused and wonder why Schilder was so highly regarded as a medical philosopher. When the author states: "I have come to the general conclusion that the size and weight of objects, the distance and dimensions of space, speed, impact and motion, become more or less the immediate expression of the total libidinous situation," the reader is inclined to consider such a sweeping generalization to be no more than a reckless assertion founded on subjective interpretations of a feeling of awe in contemplation of the cosmos. There is, furthermore, a vagueness that is unsettling. "Changes" in the vegetative system, "changes" in consciousness, "changes" in tone and in reaction movements, "changes" in the postural model of the body—

all these are mentioned, and all on the same page, without the author's describing what the changes are. No doubt he has in mind what such changes are, and in many other instances he describes them with greater precision. One must ask, however, whether this is the power of a great intellect. Perhaps facility in the expression of ideas makes them appear large precisely because they are vague.

Schilder is at his best in dealing with the ideas of others, usually in critical fashion. He thoroughly demolishes the conditioned "reflex" theory of Pavlov and proves clearly that the animal subject is responding to a total situation. He is equally critical of some of the psychoanalytic interpretations that have been advanced by followers of Freud. He approves the tenets of the gestalt school of psychology and devotes considerable space to elaborations of this theory. Perhaps his most enduring contribution is on the subject of thinking: "I am inclined to define thinking as an act directed towards objects, the performance of which is intercepted by acts directed towards other objects. This interference appears in pictures. It is characteristic of the fertile act of thinking that it reaches its goal, insight into its object relation, in spite of the breakage." He pays great attention to thought mechanisms, and yet relatively little to the affective aspects of self contemplation and to alterations of attitudes toward the self that occur constantly, and more or less rhythmically, in the normal and in the abnormal state. While highly symbolic expressions are employed, the whole discussion seems often too intellectualized to correspond with experience. Schilder is inclined to join together the types of thinking found in the primitive, the child and the schizophrenic personality, but with nothing to give precision to this dubious doctrine. On the whole, one is inclined to wonder how much of this delving into the region of the mind will survive a half-century of further penetration. Part of Freud's greatness is attributable to the simplicity of his concepts. Schilder's cannot be measured by the same yardstick.

Lincoln—Douglas: The Weather as Destiny. By William F. Petersen. Price, $3. Pp. viii, plus 305. Springfield, Ill.: Charles C Thomas, Publisher, 1943.

Lincoln was 6 feet 4 inches (193 cm.) or over; Douglas was under 5 feet 3 inches (160 cm.) and broad in proportion. Lincoln was conceived in cold, rainy weather; Douglas, in midsummer. Lincoln was close to the soil from infancy; Douglas was raised in comparative luxury. Both of them came on the scene in southern Illinois, where mortality rates for tuberculosis are still high. Petersen contrasts the careers of these two striking personalities, with the background made up of cosmic forces that pass almost unnoticed by most persons. Lincoln, in youth robust and powerful, became gaunt, and almost frail, with early manhood and was subject to periodic depressions. However, he endured a political campaign that left his opponent, "a steam engine in britches," completely worn out, and was entering into the fulness of mature vigor when Douglas wore out and died, at the age of 48.

While Lincoln and Douglas are the principal actors in this drama, Mary Todd, with her pyknic physique and her paranoid psychosis, also attracts a share of the author's attention and sympathy. These are the players, but the play is about all men and their destiny as interpreted in the light of cosmology. As the author states:

"The tragedy of our three chief actors—Lincoln and Douglas and Mary Todd ended long ago; the story, however, is valid for the rest of us. All three were Prometheans—who dared; but all had to bow to the

was differentiated as a form caused by localized lesions, usually vascular, in the basal ganglia.

From these known forms of involuntary movements, chiefly double athetosis, another peculiar type was differentiated in the first decade of the twentieth century. At a time when athetosis was widely recognized as a symptom of an organic disease process of the brain, another form was again first described as hysterical. In 1908 Schwalbe [14] reported on a disease characterized by "tonic contractions with hysterical symptoms," and Ziehen,[15] enlarging the large but ill defined group of disorders known as *degenerative Krampfneurose*, added a new form which he called *Torsionsneurose*. Oppenheim,[16] elaborating his own observations and those of Schwalbe, inaugurated the term "dystonia" in 1911 and recognized "dystonia musculorum deformans" as an organic disease of the nervous system. Motor disorders constituted the cardinal symptom of the disease, defined as an alternation between hypotonia and a tendency to tonic muscle tensions, the latter being brought on most intensively by the locomotor functions of walking and standing. The occurrence of pronounced lordosis in the majority of his cases led him to suggest the name dysbasia lordotica progressiva as an alternative.

Almost twenty years before the description of Schwalbe and Oppenheim, Gowers,[17] in 1893, described the same symptoms in a case of so-called tetanoid chorea.

There was tonic spasm which was continuous and varied by paroxysmal attacks of similar but more intense spasm . . . the arms were extended, pronated and rotated inwards, so as to bring the back of the forearm outwards while the fingers were generally slightly flexed at all joints; the feet being overextended in talipes equinovarus and the toes were flexed. At times the spasm of the hip became flexor so that the extended legs were raised off the bed. The muscles of the trunk were also involved in the spasm.

Willmanns, K.: Monographien aus dem Gesamtgebiete der Neurologie und Psychiatrie, Berlin, Julius Springer, 1926, no. 48; Das extrapyramidal motorische System und seine Erkrankungen, Fortschr. d. Neurol., Psychiat. **3**:245, 1931; Symptomatologie der Erkrankungen der Stammganglien, in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1936, vol. 5.

14. Schwalbe, W.: Eine eigentümliche tonische Krampfform mit hysterischen Symptomen, Inaug. Dissert., Berlin, G. Schade, 1908.

15. Ziehen: Ein Fall von tonischer Torsionsneurose, Neurol. Centralbl. **30**:109, 1911.

16. Oppenheim, H.: Ueber eine eigenartige Krampfkrankheit des jugendlichen Alters (Dysbasia lordotica progressiva, Dystonia musculorum deformans), Neurol. Centralbl. **30**:1090, 1911.

17. Gowers, W. R.: A Manual of Diseases of the Nervous System, Philadelphia, P. Blakiston, Son & Co., 1893.

Similar symptoms had previously been observed in cases of double athetosis, namely, the occurrence of movements of the trunk and the proximal parts of the extremities differing somewhat from athetotic movements (Ross, d'Adversen, Kurella and others, cited by Audry [11]).

In the numerous reports following the description of dystonia by Schwalbe and Oppenheim, the peculiarities of the motor disturbances were analyzed, and attention was called to the onset in childhood and the occurrence of the disease in families of Jewish-Russian descent. Features particularly striking to the observer suggested new names, such as tortipelvis and progressive torsion spasm. Eventually, Mendel,[18] in a survey of all cases recorded up to 1919, summarized the significant clinical data and created the name "torsion dystonia." He differentiated this disease from other types of involuntary movements, such as hysteria, double athetosis, chorea and myoclonus and expressed the opinion that it constituted a morbid entity. At this time "dystonia" was defined as a disease entity on the basis of clinical observations alone; the responsible cause or causes were unknown, and specific pathologic processes were not recognized. The brain of the patient described by Thomalla [19] had been examined, but the lesions observed were used by Mendel merely as evidence for the presence of an organic disease process localized in the basal ganglia.

The situation became more complicated after the appearance of encephalitis lethargica and the frequent occurrence of postencephalitic states in the 1920's. The same symptoms as those thought to be characteristic of dystonia of unknown origin could be observed in a disease which was recognized as a clinical and pathologic entity. Furthermore, in the case of Thomalla, with the symptoms of dystonia, the lesions characteristic of Wilson's disease were present in the basal ganglia. These and other observations on cerebral lesions of well known origin (birth injury; carbon monoxide poisoning) produced doubt as to the concept of a morbid entity "dystonia" and suggested that various cerebral processes might be responsible for the appearance of dystonic symptoms. At the meeting of the International Neurologic Association in Paris (1929), Wimmer [20] concluded:

Pathology has not been able to bring evidence that torsion dystonia is a disease entity. Dystonia as a

18. Mendel, K.: Torsionsdystonie, Monatschr. f. Psychiat. u. Neurol. **46**:309, 1919.

19. Thomalla, C.: Ein Fall von Torsionsspasmus mit Sectionsbefund, Ztschr. f. d. ges. Neurol. u. Psychiat. **41**:311, 1918.

20. Wimmer, A.: Le spasm de torsion, Rev. neurol. **1**:904, 1929.

DYSTONIA

I. HISTORICAL REVIEW; ANALYSIS OF DYSTONIC SYMPTOMS AND PHYSIOLOGIC MECHANISMS INVOLVED

ERNST HERZ, M.D.

NEW YORK

HISTORICAL REVIEW

During the fourteenth and fifteenth centuries epidemics of dancing occurred. They were apparently hysterical in nature, as far as can be judged from contemporary accounts. The condition finally came to be known as "St. Vitus' dance" because some of the victims recovered at the shrine of St. Vitus, in Saverne, France. This term was subsequently applied to all disorders characterized by hypermotility, whether they were neuroses or psychoses or were clearly the result of lesions of the nervous system. Paracelsus attempted an etiologic classification, differentiating "chorea imaginativa," the dancing sickness, from "chorea lasciva," caused by sexual desire, and chorea due to physical causes. Subsequently the pattern of the abnormal behavior was studied more thoroughly. Horst (1623) reported a case in which the abnormal movements did not resemble dancing but were described as simple movements of the limbs. Sydenham[1] (1685) distinguished for the first time the peculiar involuntary movements occurring in a nervous disease in children. But at the end of the eighteenth century major chorea, minor chorea and involuntary muscle activity (Wicke[2]) were not yet properly defined, and even epileptic phenomena were included with them. Bouteille,[3] in 1810, differentiated primary, secondary and tertiary chorea and described posthemiplegic chorea. Huntington[4] (1872) called attention to another well defined condition with choreic movements. The

clinical work of Ziemssen (1877) and Wollenberg[5] (1898) and the pathologic investigations of Anton[6] (1896) and Bonhoeffer[7] (1897) established the basic knowledge of the group of choreic movements and the diseases in which they occur. Another type of phenomenon was defined by Parkinson[8] (1817) when he described shaking palsy and initiated the analysis of alternating tremor and rigidity. He referred to a case reported by de Sauvages,[9] in 1795, as one of *scelotyrbe festinans*. Credit for the establishment of athetosis as a distinct form of involuntary movement in nervous disease must be given to Hammond[10] (1871), who presented pathologic changes in 1 of his cases in a later edition of his textbook. In the following years many cases of disorders with athetotic movements were reported, as can be seen in the review of *l'athétose double* by Audry[11] (1892). Double athetosis became later a fairly circumscribed entity, after C. and O. Vogt[12] described status marmoratus of the striatum as the underlying pathologic equivalent, an assumption which has since been confirmed by numerous investigations (Lotmar[13]). Posthemiplegic unilateral athetosis

1. Sydenham, T.: Observationes medicae circa morborum acutorum historiam et curationem, London, G. Kettilby, 1685.

2. Wicke, E. C.: Versuch einer Monographie des grossen Veitstanzes und der unwillkürlichen Muskelbewegung, Leipzig, F. A. Brockhaus, 1844.

3. Bouteille, E. M.: Traité de la chorée, ou danse de St. Guy, Paris, Vinçard, 1810.

4. Huntington, G.: On Chorea, Med. & Surg. Reporter 26:317, 1872.

5. Wollenberg: Zur Lehre von der Chorea, Arch. f. Psychiat. 30:676, 1898.

6. Anton: Ueber die Beteiligung der basalen Gehirnganglien bei Bewegungsstörungen insbesondere bei der Chorea, Jahrb. f. Psychiat. 14:14, 1896.

7. Bonhoeffer, K.: Ein Beitrag zur Lokalisation der choreatischen Bewegungen, Monatschr. f. Psychiat. u. Neurol. 1:6, 1897.

8. Parkinson, J.: Essay on Shaking Palsy, London, Sherwood, Neely & Jones, 1817.

9. de Sauvages, F. B.: Nosologia methodica, Leipzig, sumpt. E. B. Schickerti, 1795.

10. Hammond, W. A.: A Treatise on Diseases of the Nervous System, New York, D. Appleton & Co., 1871.

11. Audry, J.: Étude de pathologie nerveuse: L'athétose double et les chorées chroniques de l'enfance, Paris, J.-B. Baillière & fils, 1892.

12. Vogt, C., and Vogt, O.: Zur Lehre der Erkrankungen des striären Systeme, J. f. Psychol. u. Neurol. (supp.) 25:627, 1919-1920.

13. Lotmar, F.: Die Stammganglien und die extrapyramidal motorischen Syndrome, in Foerster, O., and

to Putnam, different cerebral disease processes serve as underlying causes, among which are birth injury, infections, injury to the brain and degenerative diseases.

SCOPE OF PRESENT INVESTIGATION

The last conclusions expressed by Wilson[31] show how problematic the pathogenesis of dystonia still is. He stated:

When torsion spasm appears as a symptom, it is hardly anything else than a variety of athetosis, proximal rather than distal; when it occurs in a "pure" state pathology shows that at least some cases belong to lenticular disease.

In view of this statement, many questions remain to be answered: "Hardly anything else" could mean "not quite the same"; "pure state" is not defined, and "at least some cases" does not include the majority of observations. The situation might be clarified by a consideration of the manner in which the investigation of dystonia has previously been carried on. Clinical observations with predominantly descriptive methods have resulted in the sorting out of a group of cases with a peculiar symptomatology. The original concept of a disease entity proved to be unfounded, and dystonia has since been regarded as a syndrome which occurs in various diseases. In view of the numerous investigations of the last thirty years, it seems worth while to review the collected material, both clinical and pathologic. First, dystonic symptoms and their physiologic mechanisms must be defined. Diseases in which these dystonic symptoms appear must be analyzed with respect to onset, course and accompanying disorders. In this way, in a number of cases, the clinician will be able to make an etiologic diagnosis, such as postencephalitic state, Wilson's disease (hepatolenticular degeneration), injury to the brain, infection, poisoning, tumor and arteriosclerosis. Dystonic phenomena in such conditions do not belong to the dystonia group; they constitute only a symptom, dependent on the particular localization of the process in the brain. Such conditions should be designated, for example, as postencephalitic state or Wilson's disease with dystonic symptoms. Only the remaining disorders, which cannot be placed under one of the recognized disease entities, should be grouped together as "dystonia." Since such a preliminary grouping is merely negative, the discussion of the character of the disease and the possibility that "dystonia" is a morbid entity should be postponed until uniform clinical pictures can be correlated with definite pathologic processes in the brain.

Consequently, in the following investigation I shall begin by using this classification. The cases of 15 patients who have been under observation at the Neurological Institute with a condition diagnosed as dystonia will be analyzed, and all the available cases reported in the literature will be considered. With the help of cinematographic analyses and electromyographic studies, dystonic symptoms will be defined and their mechanisms explored (part I). All cases in which well defined dystonic symptoms were present will be studied in detail, with the use of all available data. After the cases of known disease entities have been excluded, the remaining "dystonia group" will be defined (part II). The pathologic changes associated with diseases exhibiting dystonic symptoms will be reviewed, after the cases described have been classified clinically in the manner just outlined (part III). Finally, after known cerebral disease processes have been differentiated, a correlation of specific pathologic processes with clinical peculiarities of the "dystonia group" will be attempted.

DYSTONIC SYMPTOMS

FILM ANALYSIS OF CLINICAL CHARACTERISTICS

Dystonic movements belong to the group of abnormal involuntary movements associated with nervous diseases, such as chorea, ballism, athetosis, tic and antagonist tremor. Such movements are intercalated in the normal motor patterns without recognizable reason. They appear purposeless to the patient and to the observer. There is "the absence of inhibition or control which is characteristic of all involuntary movements" (Hunt[32]); in other words, there is an "excess of motion," which disturbs the posture at rest. Simultaneous disturbance of coordination and change in muscular resistance to passive movements may be present, e. g., hypotonia in cases of infectious chorea or rigidity with antagonist tremor.

By analysis of moving pictures I differentiated various forms of involuntary movements and described their characteristics.[33] Two types of "amyostatic hyperkinesis" (accepting a term first used by Strümpell[34]) were differentiated: irregular movements, including myoclonia and tic

31. Wilson, S. A. K.: Neurology, edited by A. N. Bruce, Baltimore, William Wood & Company, 1940, vol. 2.

32. Hunt, J. R.: The Static and Kinetic Systems of Motility, Arch. Neurol. & Psychiat. **4**:353 (Oct.) 1920.

33. Herz, E.: Die amyostatischen Unruheerscheinungen, Leipzig, Johann Ambrosius Barth, 1931.

34. Strümpell, A.: Zur Kenntnis der sog. Pseudosklerose, der Wilson'schen Krankheit und verwandter Krankheitszustande (der amyostatische Symptomenkomplex), Deutsche Ztschr. f. Nervenh. **54**:207, 1916; Die myostatische Innervation und ihre Störungen, Neurol. Centralbl. **39**:2, 1920.

syndrome is in no way pathognomonic; it occurs with Wilson's disease, pseudosclerosis, athetosis, Parkinson's disease and Huntington's chorea.

In 1922 Wechsler and Brock [21] had already expressed the opinion that dystonia, double athetosis and Wilson's disease could not be differentiated in some instances, and Jakob [22] (1932), after an anatomic study of 3 cases, concluded:

. . . Whether torsion dystonia is only a syndrome occurring with different disease processes in the brain or whether ,there is a morbid entity "dystonia" cannot be definitely decided. It is too early to differentiate distinct diseases.

However, in the last comprehensive description of torsion dystonia, in 1936, Mendel [23] stated:

Torsion dystonia is a well defined syndrome, like Ménière's disease. In the same way in which exophthalmic goiter can be separated from the other forms of hyperthyroidism, so a distinct position must be conceded to dystonia. With this in mind, the cases of dystonia must be included in one disease group.

Mendel did not mention in 1936, as he did in 1918, the concept of a morbid entity.

In a symposium on the basal ganglia, at the meeting of the Association for Research in Nervous and Mental Disease in 1940, the problems of dystonia were referred to in some papers. Goodhart,[24] in explaining the various types of motor disorders, spoke of "cases of the dystonic group" and of "dystonic movements" and illustrated "some of the difficulties met in making a definite diagnosis between dystonia, psychogenicity and chronic degenerative chorea." Phelps [25] and Carlson,[26] in their papers on retraining and reeducation, referred only to cases of athetosis. They apparently assumed that cases of dystonia fell under the same heading. Bucy,[27] in speaking of choreoathetosis, stated:

The term indicates an ill-defined group of abnormal involuntary movements. . . . Such a definition includes a variety of movements denominated as those of chorea, athetosis, hemiballismus, acute hemichorea, dystonia, torsion spasm, etc. etc. . . . It is obvious that accurate terminology is desirable but it has not seemed possible to achieve such a precision in the present state of ignorance of the underlying pathology and physiology.

Alexander [28] expressed the opinion that there is no fundamental difference between athetosis and dystonia. Athetoid disturbance of the extremities is called athetosis; athetoid disorders of the axial parts of the body, including the neck and trunk, are termed torsion dystonia. He stated that in his experience with the congenital bilateral form of athetosis and dystonia the one condition was never present without the other. The maintenance of two names—athetosis and dystonia—has caused a certain degree of confusion in that it suggests that these conditions may be two different diseases. But "athetosis and dystonia are one and the same disease, although difference in localization of this disease may cause one or the other symptom." Alexander suggested that the two names be used to describe the clinical phenomena but that the disease entity as a whole be referred to under the one name "athetosis." The pathologic observations of Alexander will be cited later. In this connection I wish only to stress that he drew his conclusions from cases of congenital disease alone in which status marmoratus was present as the pathologic process. Putnam [29] included in the "athetoid syndrome" athetosis and dystonia, torticollis, ballism and hemichorea. Electromyographic studies by Hoefer and Putnam [30] provided means by which these symptoms may be distinguished from antagonist tremor, whereas a differentiation of the clinically different types of the athetoid syndrome, particularly athetosis and dystonia, seems not to be possible. According

21. Wechsler, J. S., and Brock, S.: Dystonia Musculorum Deformans with Especial Reference to a Myostatic Form and the Occurrence of Decerebrate Rigidity Phenomena, Arch. Neurol. & Psychiat. **8:**538 (Nov.) 1922.

22. Jakob, A.: Zur Frage der lokalisatorischen und nosologischen Auffassung der torsionsdystonischen Krankheitserscheinungen, Deutsche Ztschr. f. Nervenh. **124:**148, 1932.

23. Mendel, K.: Torsionsdystonie, in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1936, vol. 16, p. 848.

24. Goodhart, S. P.: Cinematographic Demonstration of Types of Extrapyramidal Syndromes, with Remarks on Differential Diagnosis, A. Research Nerv. & Ment. Dis., Proc. (1940) **21:**494, 1942.

25. Phelps, W. M.: Evidences of Improvement in Cases of Athetosis Treated by Reeducation, A. Research Nerv. & Ment. Dis., Proc. (1940) **21:**529, 1942.

26. Carlson, E. R.: Treatment of Athetosis by Retraining, A. Research Nerv. & Ment. Dis., Proc. (1940) **21:**534, 1942.

27. Bucy, P. C.: Cortical Extirpation in the Treatment of Involuntary Movements, A. Research Nerv. & Ment. Dis., Proc. (1940) **21:**551, 1942.

28. Alexander, L.: The Fundamental Types of Histopathological Changes Encountered in Cases of Athetosis and Paralysis Agitans, A. Research Nerv. & Ment. Dis., Proc. (1940) **21:**334, 1942.

29. Putnam, T. J.: Treatment of Athetosis and Dystonia by Section of Extrapyramidal Motor Tracts, Arch. Neurol. & Psychiat. **29:**504 (March) 1933; Results of Treatment of Athetosis by Section of Extrapyramidal Tracts in the Spinal Cord, ibid. **39:**258 (Feb.) 1938; Athetosis, Yale J. Biol. & Med. **11:**459, 1939; Neurologic Aspects of Spasticity and Athetosis, New York State J. Med. **41:**1822, 1941; The Operative Treatment of Diseases Characterized by Involuntary Movements, A. Research Nerv. & Ment. Dis., Proc. (1940) **21:**666, 1942.

30. (a) Hoefer, P. F. A., and Putnam, T. J.: Action Potentials in Athetosis and Sydenham's Chorea, Arch. Neurol. & Psychiat. **44:**517 (Sept.) 1940. Hoefer, P. F. A.: Physiology of Motor Innervation in the Dyskinesias, A. Research Nerv. & Ment. Dis., Proc. (1940) **21:**502, 1942.

ments and is less evident in the faster movements. Obviously, the activity of antagonist groups limits the rapidity of the movement.

Dystonic Movements.—Slow, long-sustained turning movements of the head and trunk and rotations of the upper or lower extremities were analyzed as dystonic movements. Besides these movements with a twisting effect, there were slow sustained tensions in the platysma muscle, the shoulder muscles, the pectoralis muscle and the muscles of the leg and foot. The head and trunk are most frequently involved, as will be demonstrated later in the description and film analyses of my own observations.

(one sixteenth) of a second. Sustained tension may be interposed between other movements, with interruption and alteration of their course. The series in figure 4 shows the continuous record for a swinging movement of the right arm. From frame *1* to frame *8* the arm swings backward; from frame *9* to frame *13* the arm goes to a halfway position, and stays there from frame *13* to frame *23*. From frame *24* to frame *30* the forward swing continues. From frame *31* to frame *38* the arm swings backward; at frame *39* the forward movement starts again. During the course of an alternating swinging movement of the whole arm, tension arrests the

Fig. 2.—Sustained contraction of the platysma muscle.
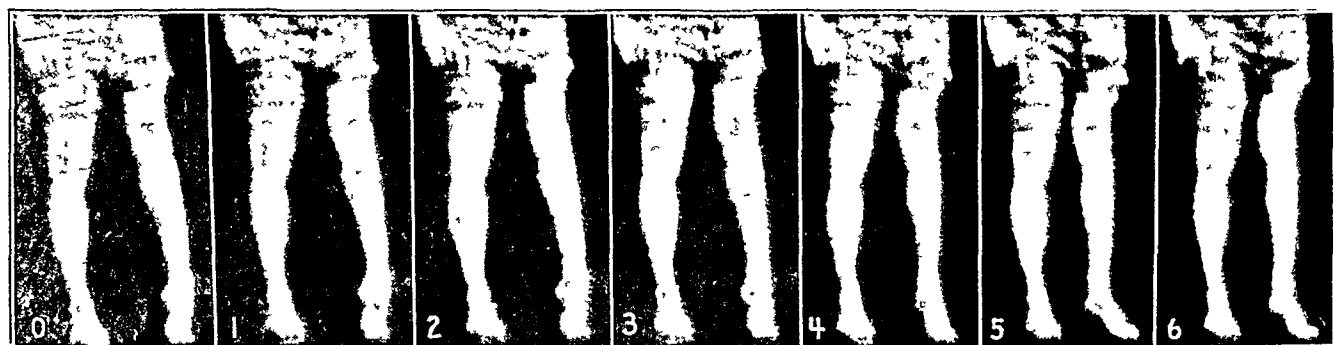
Fig. 3.—Sudden relaxation of long-sustained plantar flexion of the foot between frame *3* and frame *4*.

The course of the dystonic movements was found to be as characteristic as that of athetosis. The tightening and stiffening of the affected part could be seen before and during the movement and after the end of the motion proper, with the effect that the end position was maintained for a long time. In the film series shown in figure 2, contraction of the platysma muscle was completed in 6 frames, the end position being maintained from frame *6* to frame *83*, that is, almost five seconds, before the tension relaxed. How powerful the increase in tension may be can be seen in figure 3. The left foot was kept in extreme plantar flexion and inversion against the weight of the body for several minutes. As soon as the tension relaxed (which occurred suddenly, between frame *3* and frame *4*), the foot was pushed down in a small fraction

swing for 10 frames and keeps the arm in an intermediate position. After the tension ceases, the alternating movements are continued.

The occurrence of particularly long-sustained tensions may be taken arbitrarily as the distinguishing characteristic of dystonic movements. The tensions are responsible for the slow course of the movements and the long-sustained intermediate or end positions. Between athetotic and dystonic movements there is only a quantitative difference in the degree of tension, that is, in the amount of simultaneous activity of antagonists. Both forms of abnormal involuntary movements, athetotic and dystonic, constitute a group of irregular sustained movements, characterized by tensions before, during and after the motion proper.

twitchings, chorea, ballism, athetosis and torsion, and regular movements, including antagonist tremor and myorhythmia, and hyperkinesis, characterized by a complicated pattern. The turning and twisting character of some irregular movements induced me to suggest the term "torsion," but because of their predominant occurrence in cases of dystonia the term "dystonic movements" is more convenient.

Athetotic and dystonic movements show definite similarities. For that reason dystonic movements have frequently been referred to as proximal athetosis. As in my previous analysis, the mechanisms involved in athetotic movements may be described first.

Athetosis.—Characteristic of athetosis is the course of a single athetotic movement. In a simple voluntary movement, as well as in a choreic movement, the moved part is continuously shifted from one position to another. The athetotic movement does not take the same continuous course from the beginning to the end of the movement. First, tightening and stiffening of the affected part set in without a visible excursion. After a while the movement starts, and then the movement of the part is usually continuous to the end point. In an athetotic extension of the big toe the protruding, tightened tendon of the extensor hallucis longus muscle could be seen in 2 frames before the proper athetotic movement of the big toe started. But the course of the athetotic movement is not always continuous, even after the proper movement has started. Particularly in movements with larger excursions, the moving part sometimes stays in an intermediate position for a period represented by a few frames. At the end point of the movement the position is usually maintained until the moved part relaxes. The time relations of these peculiarities can be studied by comparison of single frames of consecutive moving pictures (16 frames represent one second at usual speed, and 64 frames, one second at slow motion). The series in figure 1 shows an athetotic extension of the index finger. At *0* the index finger was tightened, and at *3* (in three-sixteenths second) the extension was completed. The extension was maintained for 14 frames (almost a second), until suddenly, between frame *17* and frame *18*, the index finger became visibly flaccid.

The time consumed by the athetotic movement, from the beginning of the movement proper to the end position, is not remarkably greater than that consumed by a comparable choreic movement. The athetotic movement appears slower only because the time which the tension consumes at the beginning and at the end of the

proper motion is included in the calculations. There are surely resemblances between chorea and athetosis. But it is doubtful whether "the resemblances are more impressive than the differences" (Wilson,[31] Hoefer and Putnam[30a]). At any rate, real differences between the two kinds of involuntary movements are distinctly evident in the analysis of the two clinical phenomena. Athetotic movements consist not only of motion from one position to another but of a fac-
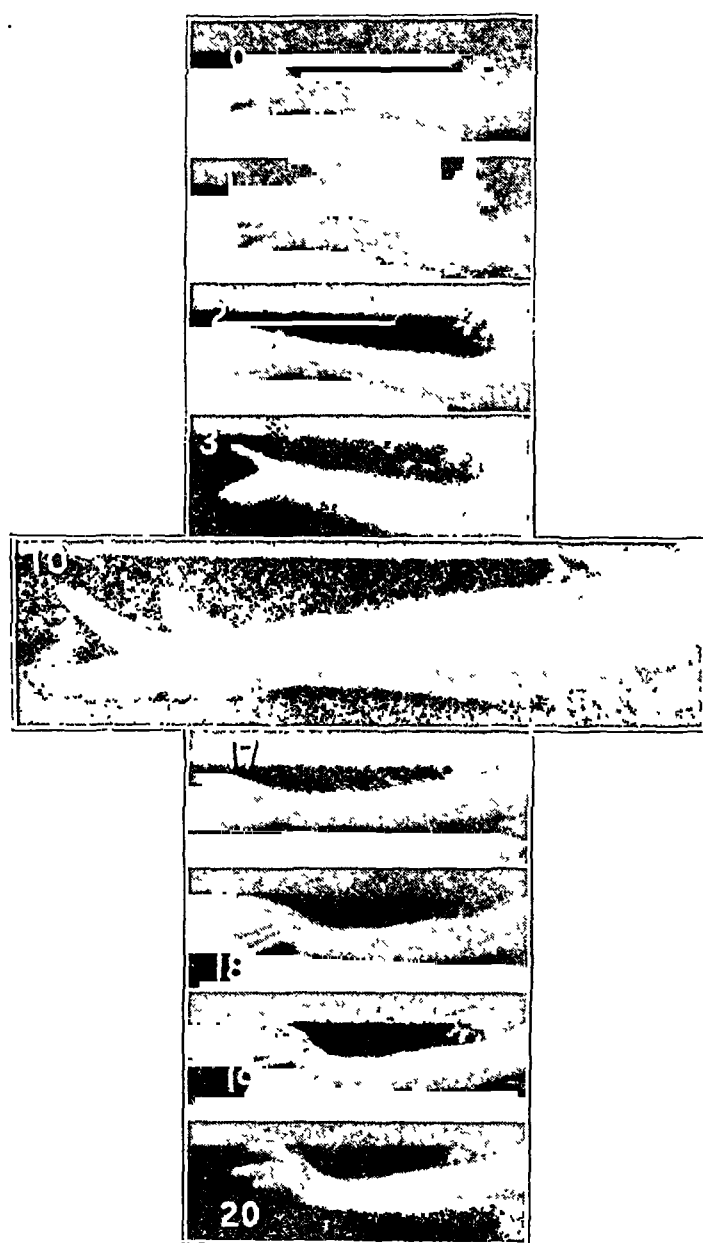
Fig. 1.—Athetotic extension of the index finger. Note the sudden release of tension between frame *17* and frame *18*.

tor with a stiffening and tightening effect, which increases the tension of the affected moving part. The character of the latter factor will be discussed later. At this point tension means only a visible and sensible condition of the muscles involved in the involuntary movement. The two factors of motion and tension vary in intensity from one case to another. There is always an inverse relation between the degree of tension and the speed of the athetotic movement. The tension is more pronounced in slower athetotic move-

Some observations indicate that various anatomic structures influence the tendency to tension and the hyperkinetic impulses. In case 13, to be described in part II of this study, there were dystonic movements of the left arm which showed extremely severe tension and little excess motion. Figure 16 *A* (part II[35]) shows the left arm in long-sustained extension and adduction. When the patient turned around and walked (fig. 16, *B* and *C*[35]), the arm was slowly flexed and adducted, and in all positions the hand was flexed and closed. A cortical operation was performed, and the right prefrontal arm area was excised. After the operation there was a striking reduction of tension; the arm was much more freely movable (fig. 16 *D*[35]), and involuntary movements of the hand and fingers appeared (*D*). The improvement after the operation in this case resulted particularly in decrease of tension. The reduction of tension after the anterolateral chordotomy in case 9 can be seen in figure 12.[35] The patient in case 2[35] (compare the preoperative and the postoperative picture in figure 7 of part II) described the reduction of tension and the feeling of stiffness as the notable result of the chordotomy.

Dystonic Postures.—These peculiar positions, which occur in various combinations, will be described and illustrated later. One may better understand the mechanism involved in their production by reference to the significant features seen during the development of this crippling symptom as the disease progresses.

Drawing tensions in the back or the upper or lower extremities are first felt only subjectively, not infrequently as painful sensations. In the beginning of the disease this cramplike feeling is not accompanied by a visible motor effect. Later, interference with voluntary motor activity appears. The gait is hampered by tension in the leg or foot; "writer's cramp" may be an early sign. As the disease progresses, the position of the affected part becomes visibly altered. The foot may become inverted and plantar flexed and remain in this position when the patient is walking. At this time tensions result only in transient changes of position, which are maintained for a longer or a shorter period but are completely compensated. This fact has not always been realized, particularly in the case of longer-lasting postures. But in motion pictures taken over a period it could sometimes be observed how the posture was brought on by a corresponding movement and the end position was then maintained indefinitely. In the same way, the sudden disappear-

ance of a presumably permanent, but only long-maintained, posture could be seen. Frequently postures are indeed maintained for such a long period that their onset and disappearance cannot be observed and are therefore completely neglected. In more advanced conditions the posture persists during the whole day, though the degree of distortion may vary, and disappears only during sleep. Persistent contractures in peculiar positions which are not reduced even during sleep are present only in advanced conditions with secondary contractures of tendons and muscles or changes in the skeletal system.

Thus, finer analysis of different degrees of dystonic postures proves that they are brought on by dystonic movements. The characteristic tensions are maintained over such an extremely long period that the impression of a motor act is eventually lost. If twisting activity of the trunk or extremities is maintained for seconds or for a few minutes only, the motor activity is registered as a dystonic movement. If the maintenance of the end position lasts for hours, the phenomenon is spoken of as a dystonic posture. In principle, a dystonic posture is merely an indefinitely sustained dystonic movement; it is the frozen product of such a movement. The same mechanisms are responsible for the production of the two phenomena.

MECHANISMS INVOLVED

From the facts brought out by the film analysis, one may draw some conclusions with respect to the different mechanisms involved in production of the varieties of irregular involuntary movements associated with various nervous diseases. As has already been stated, in all the abnormal involuntary movements there must be assumed an "excess of motion" which produces this abnormal spontaneous motor activity. In choreic movements this overflow of motor activity appears in pure form producing movements which closely resemble voluntary motor activity. In athetotic, and still more notably in dystonic, movements another factor changes the normal continuous course of simple movements, such as are seen in voluntary activity. "Excess of tension" results in stiffening and tightening of the affected muscles and produces changes in the course of the involuntary movements and maintenance of the end position. In the case of dystonic postures only finer analysis can demonstrate excess of motion; an almost continuous excess of tension prevails.

Figure 5 demonstrates graphically the degree of influence of the two factors in various involuntary movements. *Choreic movements* are due to excess of motion without remarkable excess of tension. *Athetotic movements* derive

35. Herz, E.: Dystonia: II. Clinical Classification, Arch. Neurol. & Psychiat., this issue, p. 319.

Fig. 4—Arrest of swinging movement of the right arm by tension. In frames *1* to *8* the arm swings backward; in frames *9* to *13* the arm comes to a halfway position as it swings forward; in frames *14* to *23* it is arrested in this position; in frames *24* to *30* it continues to swing forward; in frames *31* to *38* it swings backward, and in frame *39* the arm starts to swing forward again.
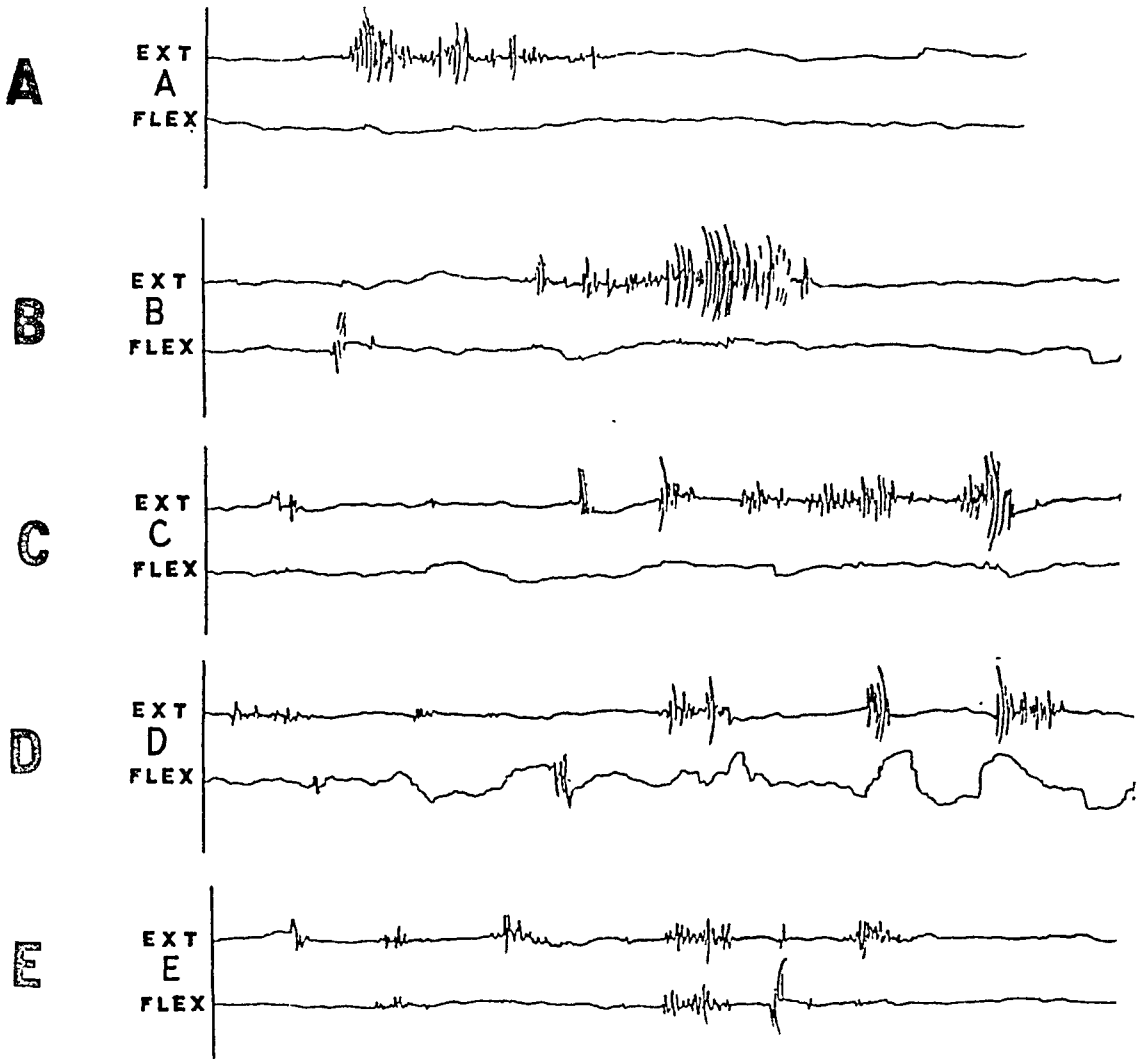
Fig. 6.—Electromyograms in a case of Sydenham's chorea.
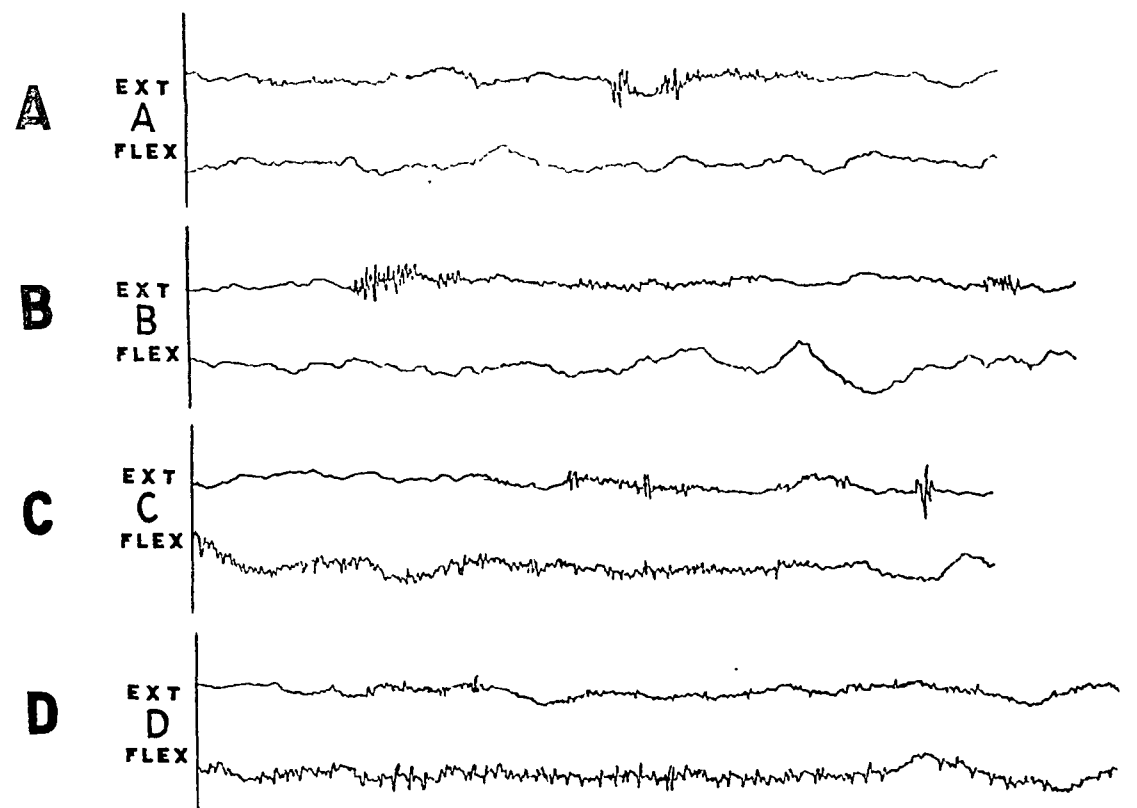
Fig. 7.—Electromyograms in a case of Sydenham's chorea.

their significant features from the approximately equal participation of excess of motion and excess of tension. In some instances the excess of motion prevails over the excess of tension. *Dystonic movements* show a still more pronounced excess of tension, which prevails over the excess of motion. *Dystonic postures* show the influence of excess of tension in almost pure form, whereas the excess of motion is scarcely noticeable.

Electromyographic Studies.[36]—Patterns of innervation vary with the forms of irregular abnormal involuntary movements. Hoefer and Putnam [30a] gave an extensive analysis of the management of muscle contraction associated with these disturbances. In the studies with coaxial needle

EXCESS OF MOTION

CHOREIC MOVEMENTS

ATHETOTIC MOVEMENTS

DYSTONIC MOVEMENTS

DYSTONIC POSTURES
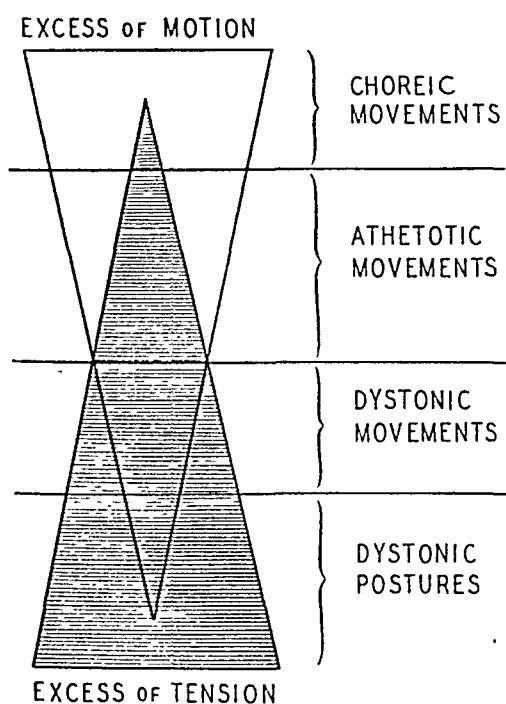
EXCESS OF TENSION

Fig. 5.—Distribution of "excess of motion" and "excess of tension" in different forms of irregular abnormal involuntary movements.

electrodes, local activity varied from single unit discharges to discharges of larger groups of units. Motor unit discharges were asynchronous and polyrhythmic, just as with normal voluntary innervation. The management of the antagonists was remarkable in that "antagonists were in almost constant, simultaneous innervation."

Obviously, this simultaneous activity of agonist and antagonist is responsible for the excess of tension observed in athetotic and dystonic symptoms. Oppenheim [16] stated that in cases of athetosis palpation revealed that antagonists were under tension. Wilson [37] found in mechanical tambour tracings that antagonists remained

"definitely contracted." Hoefer [38] gave the following explanation:

It is easy to conceive that movements must be arrested in a limb when all antagonist groups are simultaneously and maximally active or when a single muscle, such as the sternomastoid, by maximal sustained contraction holds the head and neck in an extreme position in relation to the trunk.

Hoefer, confirming Wilson's statement that "resemblances are more impressing than differences," did not differentiate between the different varieties of irregular involuntary movements. He spoke only of "more or less sustained irregular movements" and stated that "the simultaneous activity of antagonists may be steady or irregular in either muscle." From these statements it may be assumed that differences in types of innervation are present in the various irregular involuntary movements. It must be considered whether these differences in types of innervation are related to the more or less pronounced excess of tension in choreic, athetotic and dystonic movements.

Records will demonstrate the possibilities of differentiation.

Figure 6 shows records of a girl 14 years of age with Sydenham's chorea. Electromyograms were recorded with surface leads from the extensor and flexor groups of the forearm. The activity consists in short, irregular groups of waves or in bursts of longer duration in either the extensor or the flexor group. These records of electrical discharge found exclusively in one muscle group, as shown in *A, B, C* and *D* of figure 6, form 80 to 90 per cent of the recorded activity. In only a low proportion of instances did electrical activity appear in both antagonist groups, and in these instances the activity of one group was always predominant (fig. 6 *E*).

Figure 7 shows the records of a girl aged 13 years with Sydenham's chorea. The arrangement of surface electrodes on the extensors and flexors of the forearm was the same as that for the tracings in figure 6. Low voltage activity of shorter or longer duration was predominant in one group, while the antagonist did not show any activity (fig. 7 *A* and *B*). In one long-lasting burst both antagonists were involved, but the activity of the flexor group was much more intense and continuous than the activity of the extensor group (fig. 7 *C* and *D*).

In figure 8 are records of the electrical activity associated with athetotic and dystonic movements. These records were taken with surface electrodes. They confirm completely the statement of Hoefer and Putnam [30a] of the simul-

36. Dr. J. C. Price assisted me in this part of the paper, and Dr. Paul F. A. Hoefer gave me permission to use electromyographic records in his department.

37. Wilson, S. A. K.: Modern Problems in Neurology, New York, William Wood & Company, 1929.

38. Hoefer, P. F. A.: Innervation and "Tonus" of Striated Muscle in Man, Arch. Neurol. & Psychiat. 46:947 (Dec.) 1941.

and of flexion at the elbow and wrist. Records G and H (case 4) show a continuous flow of activity in the flexor group, whereas the intensity of activity in the extensor group is fluctuating.

If one pays particular attention to the electrical activity of antagonist muscles during irregular abnormal involuntary movements, one notes differences between choreic and athetotic-dystonic movements.

Choreic movements and voluntary movements show no difference in their appearance, particularly no excess of tension. Their electromyographic records are alike; likewise, Hoefer and Putnam [39] pointed out:

. . . The electromyographic records during simple normal voluntary movements presented only activity in the protagonist and no activity in the antagonist. With maximal innervation a small amount of activity appears in the lead from the antagonist too.

Altenburger [40] explained further that the onset of some activity in the antagonist depends on

found in a case of chorea "activity in the flexor muscles alone, while the extensor was at complete rest." Hoefer recorded in another case of chorea "simultaneous irregular activity, exactly as in athetosis." In a case of infectious chorea I noted some sustained contractions between the choreic movements. Figure 9 shows such sustained tension of the muscles of the thigh, which interfered with gait. The sustained extension in the swinging leg produced the stiltlike gait. But this sustained activity is infrequent in cases of chorea.

The records taken from two antagonist muscles in cases of athetotic and of dystonic movements show simultaneous activity in the agonist and in the antagonist and thus confirm the observations of Hoefer and Putnam.[30a] As these forms of involuntary movement are characterized by a greater or less degree of excess of tension, it might be assumed that this excess of
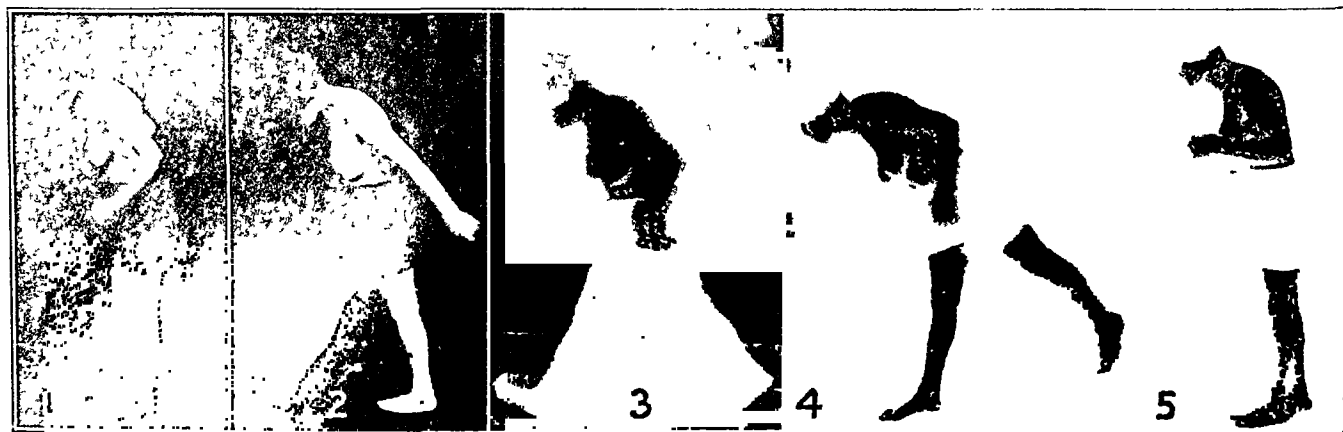
Fig. 9—Sustained contractions of the extensor muscles of the thigh during walking in a case of Sydenham's chorea.

accompanying conditions; speed and extent of the voluntary movement are of influence, and loose (*lockere*) and stiff (*versteifte*) movements show more or less simultaneous activity in both the agonist and the antagonist. In cases of chorea predominant electrical activity in the agonist and less activity in the antagonist are to be expected. This is seen in my records (figs. 6 and 7) of activity of antagonist muscles in 2 cases of chorea. Either action potentials were present in one of the muscles exclusively, or the electrical activity of the antagonist was apparently less than that of the agonist. This confirms an observation of Hoefer and Putnam,[30a] who also

tension is due to the simultaneous activity of the two antagonist muscles. Further analysis of the electromyographic records and their comparison with the clinical characteristics of involuntary movements will be possible after moving pictures and electromyograms have been taken simultaneously and synchronized.

Electrophysiologic analysis of normal posture (Wachholder and Altenburger [11]) shows a complicated pattern of muscle activity, which varies in accordance with the conditions involved. Particularly intricate is the question of relaxation. Some, but not all, people are able to bring a part of the body into a relaxed position in which no activity can be recorded from either the agonist or the antagonist. The adaptation of the various

39. Hoefer, P. F. A., and Putnam, T. J.: Action Potentials of Muscles in Normal Subjects, Arch. Neurol. & Psychiat. 42:201 (Aug.) 1939.

40. Altenburger, H.: Elektrodiagnostik (einschliesslich Chronaxie und Actionsströme), in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1937, vol. 3.

41. Wachholder, K., and Altenburger, H.: Willkürliche Haltungen, Arch. f. d. ges. Physiol. 212:657, 1926.

taneous irregular innervation of the agonist and the antagonist. Records *A* (case 2 [35]) and *E* (case 4 [35]) show simultaneous activity in the flexor and in the extensor group of the thigh and

simultaneous activity as that shown in record *B* was present almost exclusively. Record *D* (case 14) shows, again, simultaneous activity in the two antagonists, but the intensity of the flexor muscles
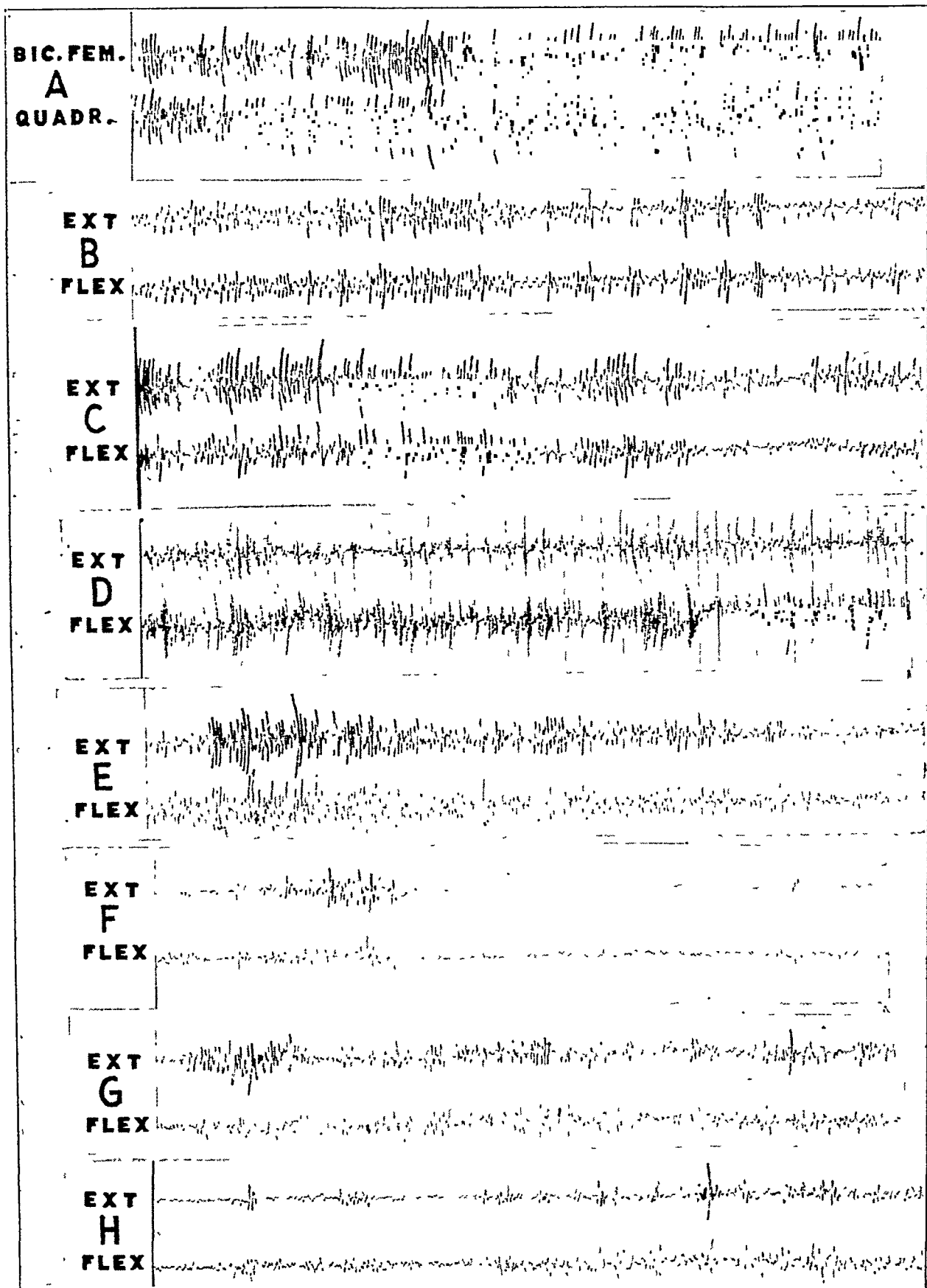
Fig. 8.—Electrical activity associated with athetotic and dystonic movements.

the forearm respectively. The intensity is equally maintained over a long period. The same simultaneous activities of equal intensity are found in a shorter burst (record *F*, case 4). During the severe hyperkinesis in case 11, such

is higher than that of the extensor muscles. This is in accordance with the clinical observations (see protocol and film analysis), for the arm of the patient was in continuous tension and was held in a position of adduction at the shoulder

The mechanisms involved in the production of this abnormal involuntary motor activity are, of course, concerned in functions of the normal motor apparatus. One is used to regard these symptoms as "release phenomena," i. e., as excessive, exaggerated activity liberated by the destruction of higher, regulating centers, as suggested by Vogt.

Goodhart and Tilney [42] expressed the opinion that two principal mechanisms might be involved in producing the normally balanced motor function:

> . . . A kinetic mechanism is represented by a neural apparatus capable of correlating the impulses necessary to the production of purposive movements, attitudes and postures, ultimately giving these their proper motor expression. It, so to speak, prescribes and produces movements and postures for which reason it is a *kinethetic* system (causing motion).
>
> The static mechanism is represented by a neural apparatus capable of correlating the impulses necessary to the proper maintenance of postures. . . . The static mechanism . . . controls the postures which follow movements like shadows, stabilizing them through all their phases. In this sense and because it maintains posture, it is a *statothetic* system.

Similar concepts expressed by Hunt [32] were based on the theory of a double motor innervation of the muscle, an assumption which has since been proved to be erroneous. The various influences are transmitted from various structures of the brain responsible for normal motor activity to the anterior horn cell and are transferred to the muscle by the final common path.

Kinetic and static functions are so intricate and so intimately interwoven that they are difficult to separate. It seems more promising, therefore, to refer to more primitive motor functions in trying to explain the basic disturbances of the varieties of involuntary movements, and to speak of "excess of motion" and "excess of tension."

Excess of motion, which is present in all forms of hyperkinesia, both in nervous and in mental diseases, can be regarded as a disorder of the motor initiative. The normal motor behavior depends on internal (mental and physical) and external stimuli which result in a change from a condition of rest to one of motion. In hyperkinesias associated with mental disease the release of excess of motion produces a more complicated motor pattern. In nervous disease more primitive motor functions are released, and only patterns of simple movements and innervations are carried out. Kleist [43] asserted that the primitive innervations of abnormal involuntary movements associated with nervous disease are liberated constituents (*Bausteine*) of normal and synergistic movements.

The mechanism of tension, with its stiffening effect, is significant in normal motility also. Holmes [44] in describing postural fixation, drew attention to this function: "Its influence is greater at the proximal joints when the weight and momentum of the moving limb particularly require steadying by tonic contraction of the muscles around them." If the frequently misleading term "tonic contraction" is replaced by that of "sustained tension," the same mechanism which was pathologically exaggerated in dystonic postures and movements is apparent here. Those long-sustained contractions of the trunk and proximal parts of extremities referred to by Holmes have the same distribution as dystonic symptoms. This, of course, is not an accidental coincidence; the preformed mechanism of sustained muscular activity is pathologically increased predominantly at the site of its normal occurrence.

42. Goodhart, S. P., and Tilney, F.: Bradykinetic Analysis of Somatic Motor Disturbances, Neurol. Bull. **3**:295, 1921.

43. Kleist, K.: Zur Auffassung der subkortikalen Bewegungsstörungen, Arch. f. Psychiat. **59**:790, 1918; Paralysis agitans, Stammganglien und Mittelhirn, Deutsche med. Wchnschr. **51**:1725, 1768 and 1813, 1925; Bewegungsstörungen und Bewegungsleistungen (Myostase und Psychomotorik), Naturwissenschaften **15**:50, 1927; Gehirn-Pathologie vornehmlich auf Grund der Kriegserfahrungen, Leipzig, Johann Ambrosius Barth, 1934.

44. Holmes, G.: The Cerebellum of Man, Brain **62**:1, 1939.

mechanisms of posture to forces outside the body is made possible by different factors, c. g., by increase in number of the affected motor elements of a muscle or by a shift in activity from one part of a muscle to another. In the maintenance of posture, it is most important to "strut" joints, and thereby to connect two parts so closely that they form a steady support. This union is brought on by the simultaneous and maintained activity of antagonist groups of muscles. This stiffening activity in the maintenance of normal posture resembles the sustained tensions of dys-

of the back of a patient with dystonic posture (case 3 [35]). The trunk and the upper part of the body were bent to the left when the patient was standing. Corresponding to this position there was continuous activity of the erector muscles of the left side of the trunk (records *A*, *B* and *C*). Most of the time the muscles on the right side did not show any activity. An occasional discharge from the right side (record *C*) may have been due to balancing movements. As soon as the patient lay in a prone position (record *D*, interruption at the vertical line), the abnormal
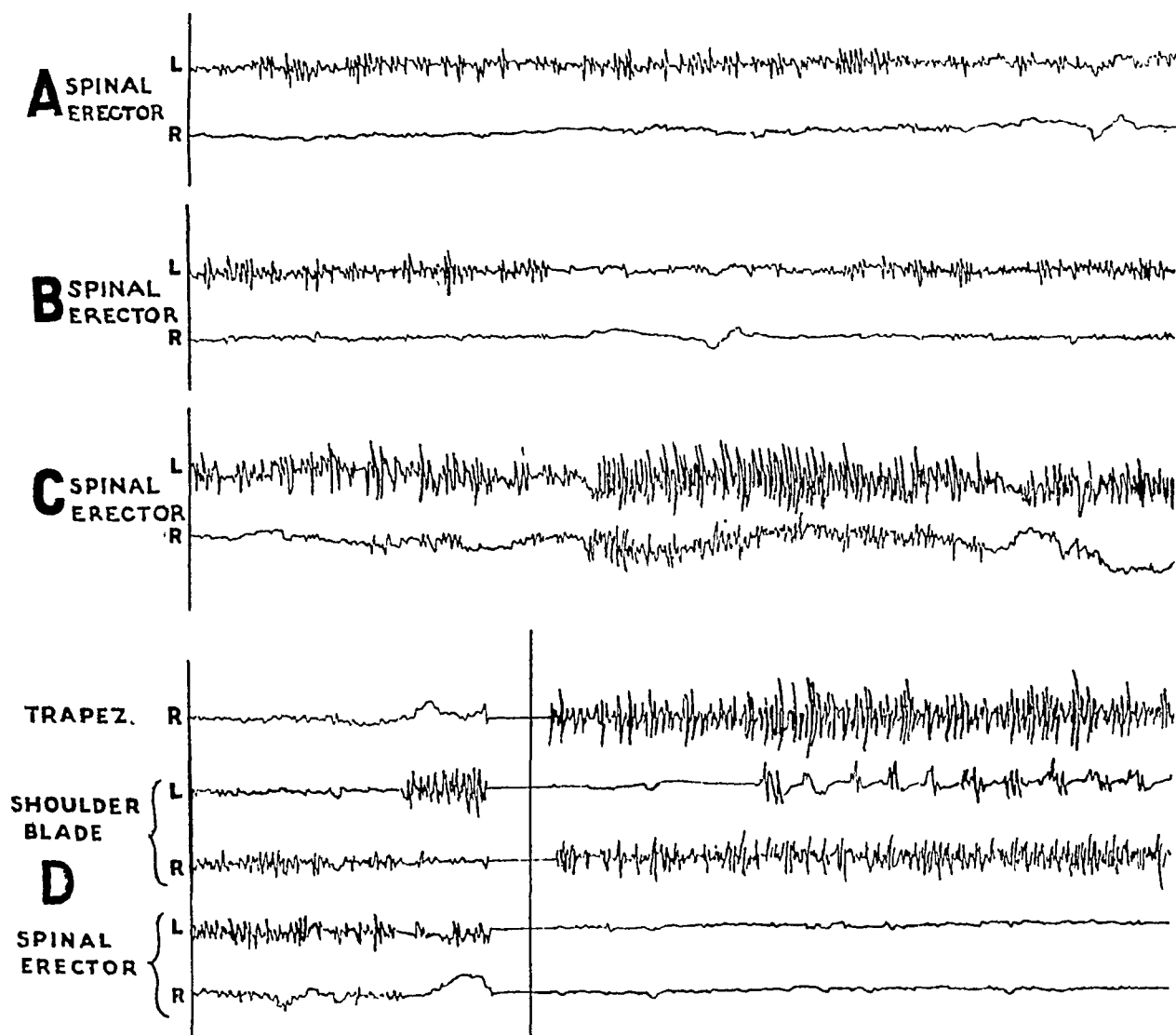
Fig. 10.—Electromyographic record of the muscles of the back of a patient with dystonic posture. After an interruption, shown by the vertical line, the patient lay in a prone position.

tonic postures. In both forms muscular activity is sustained for a long time.

Characteristic of dystonic posture is the appearance of such long-sustained muscle tensions without regard to any postural plan and with a peculiar distribution. Just as dystonic movements appear purposeless and interfere with motor behavior at rest and during voluntary activity, so tensions producing dystonic postures are not governed by the necessities of normal posture, but are mingled with postural motor innervations.

Figure 10 shows electromyographic records taken with surface electrodes from the muscles

posture and the bending of the trunk disappeared, and no electrical activity was found on either side. At the same time involuntary activity persisted in other muscles (the right trapezius muscle and the muscles of the right and left shoulders).

This record demonstrates that dystonic postural disorders are due to maintained motor innervations, as are dystonic movements. There is no important difference between these two phenomena; characteristic of dystonic posture is only the appearance of particularly long-sustained muscular contractions.

head was long maintained (fig. 1 *B* and *C*). Then, simultaneous with the turning of the head to the right, there were sustained elevation of both shoulders and

backward extension of the right arm. The end position was maintained for some time; then the tension was released again, and the head was first turned to the left. After a few moments the head was hyperextended and then bent far to the right and kept in this position. At the same time the trunk was bent forward. There were no involuntary movements of the face.

A close-up view of the hands revealed three kinds of motor phenomena:

1. Long-sustained dorsiflexion of the wrist and long-sustained extension of the fingers at irregular intervals. The periods of maintenance in the end position were always different, as were the intervals before onset of the tensions.

2. Alternating flexion and extension of the hand and fingers at apparently irregular intervals. Figure 2 shows alternating flexion and extension of the left hand at the wrist. Flexion was always followed by extension, but the end point of extension was maintained for varying lengths of time. The single frames showing extension, flexion and the maintained end position were counted and the data outlined in figure 3. The alternating units (extension and flexion) followed one another at completely irregular intervals (5—15—5—7—14 frames).

3. Rapid opening and closing of the hand. During the closure there was the synergic dorsiflexion of the hand at the wrist. Figure 1, series *E*, shows closing of the hand in three frames (between frame *4* and frame *6*), instantly followed by opening, which appears in three frames (between frame *7* and frame *10*). The whole cycle was completed in less than half a second

A close-up view of the lower extremities showed alternating movements of the left leg and swinging movements of both legs, interrupted by long-sustained extension of the lower part of the right leg, with flexion at the hip. The feet were usually kept in a pes cavus position—in extreme plantar flexion and inversion. The plantar flexion relaxed sometimes for a few moments, especially in the left foot. There was extreme plantar flexion of the toes.

The patient was skilful in drinking water out of a paper cup (fig. 1 *D*). When sitting on a chair, he tried to keep his body as steady as possible by grasping the back of the chair with the left hand and pressing the upper part of his body against the table.

Motion pictures taken after operation showed no significant change in the position of the head, trunk and extremities. No visible difference in the tensions or the involuntary movements was observed.

A child of a healthy family, without a history of injury at birth, developed perfectly up to the age of 8 years, when motor disorders began. Sustained tensions in the right foot were the first symptom. They came on as associated movements during walking and produced a peculiar position of the foot. Gradually the same disorder affected the whole right lower extremity. Then the postures produced by the tensions were maintained from several minutes to a few hours; later they became permanent, and finally the trunk, neck and all four extremities were involved.

In addition to these dystonic movements and postures, more rapid involuntary movements appeared and interfered with voluntary action
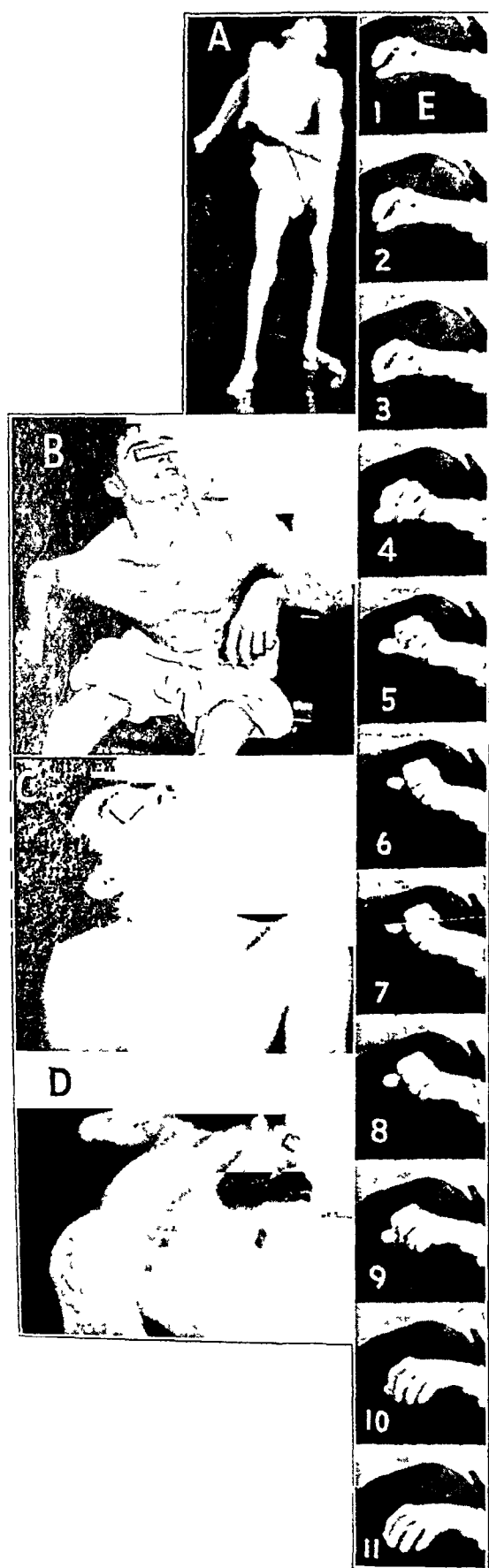
Fig. 1 (case 1).—*A*, patient standing; *B* and *C*, close-up view of head and upper part of body; *D*, patient drinking water; *E*, rapid opening and closing of hand.

DYSTONIA

II. CLINICAL CLASSIFICATION

ERNST HERZ, M.D.

NEW YORK

It has previously been pointed out that the diagnosis of "dystonia" has been indiscriminately applied to all cases in which dystonic symptoms appear. Dystonia defined in this way was, therefore, to be regarded "merely as a variety of extrapyramidal disease whose motor disorder is predominantly dystonic in order, rather than a distinct clinical entity" (Keschner).

In principle, the indiscriminate grouping together of conditions with different causes hampers further investigation. The concept of a cerebral disease entity should always be based on the occurrence of a well outlined constellation of clinical symptoms produced by a distinct pathologic process affecting certain structures of the brain. As long as the clinical picture of dystonia cannot be correlated with a definite pathologic lesion, the function of a preliminary clinical investigation is to establish clinical groups which are as homogeneous as possible; later one may try to correlate this preliminary clinical grouping with the pathologic lesions.

In the following 15 cases of patients who were examined and treated at the Neurological Institute of New York between 1940 and 1942, dystonic symptoms were present and the diagnosis of "dystonia" was considered. Motion pictures and electromyographic records were taken for analysis of the motor disorders. Detailed analyses of the films will illustrate the motor phenomena described. The onset, development and course of the disease were taken into consideration, and conclusions were based on all the clinical data available. Special attention was paid to certain distinct entities within the dystonia group.

REPORT OF CASES

CASE 1.—*History.*—J. W., a white man, was 24 years of age at the time of his admission. The family history was noncontributory. Delivery had been spontaneous, after a normal, full term pregnancy. His early development was normal.

At the age of 8 years he began to walk with his right heel raised from the ground. He was able at times to force the heel to the ground voluntarily, but the foot soon resumed an extended position. In the

following month he began to have periods of contraction of the muscles of his right lower extremity, which produced spontaneous flexion of the thigh and leg, lasting for several minutes to a few hours; soon his leg remained permanently in a flexed position except when forced in extension. A year later the left upper and lower extremities were involved, and a few months later the right upper extremity was affected. At about the same time he began to have widespread movements of all the extremities, in addition to the tonic contraction, and during the succeeding years various muscles of the trunk and neck gradually became involved.

Beginning in 1926, over a period of several years, he underwent a series of operations to relieve the contractures at the hips, knees, ankles and right wrist. The involuntary movements and tensions persisted and greatly limited the patient's activity. But he managed courageously to overcome these difficulties, and could even use the typewriter. He became an accomplished linguist and spoke seven languages.

Examination.—Physical inspection revealed pronounced scoliosis of the spine, contractures of the extremities and operative scars. There was notable wasting of the lower extremities. The hand grasp was fairly good. The reflexes were normal, and there was no sensory loss.

Mental examination revealed that he was intelligent and alert and had made an excellent adjustment to his illness.

The results of laboratory tests were normal.

Operation.—A laminectomy was performed, and the anterior column between the second and the third cervical segment on the right side was cauterized. The motor roots of the second cervical segment were crushed bilaterally.

Film Analysis.—When the patient was standing (fig. 1 A), the head was hyperextended far backward, turned to the right and bent to the left. There were extreme lordosis and kyphoscoliosis, with turning of the trunk to the left. The right shoulder was higher than the left. The right arm was kept behind the back; the left arm was adducted and flexed at the elbow, and the left hand and fingers were flexed. The lower extremities were held apart and extended. Both feet were in plantar flexion and inversion. The patient had difficulty in keeping his balance; he swayed about; the twisting torsion of the trunk increased, and there were alternating flexion and extension of the left arm with swinging movements of the leg and the whole body. He was able to stand only for a short while and then had to be supported.

Slow motion pictures revealed slow, sustained twisting movements of the trunk and swinging movements of both arms at irregular intervals, turning of the head and alternating flexion and extension of the forearms and hands.

A close-up exposure of the head and the upper part of the chest showed that the twisted position of the

319

The anterolateral chordotomy did not visibly influence the involuntary movements or the posture. Differences between the side of operation (right) and the left side could not be seen in the motion pictures.

CASE 2.—*History.*—B. R. was first admitted to the hospital in 1930, when she was 10 years old. At this time she gave a history of onset of deformity of the left ankle with limp in November 1929. There were also attacks of rigidity, mild choreiform movements of the hands and dystonic movements of both lower extremities. She stood only with support. There was pronounced scoliosis with the convexity to the right.

She was again admitted in 1937, with a history of progression of the disease during the interval. There was deformity of the right side of the chest, with the thoracic cage along the anterior axillary line, so that this side of the chest was collapsed laterally. She walked by hunching along two or three steps at a time, when she was unable to support herself longer. She could go rather rapidly in a sliding run, better than in walking. There was notable increase of strength in the muscles of the upper extremities, the shoulder girdle and the neck. The muscles of the legs were decreased in bulk, but strength was better than the size would lead one to suspect. The voice was of variable huskiness, but words were clearly enunciated at times. The only reflexes elicited were the abdominal reflexes, a weak biceps reflex in the right arm and a normal ankle response on the right. The pupils, when observed obliquely in indirect light, had a green appearance, but no Kayser-Fleischer ring was noted. The tongue was extremely long, and the patient was able to protrude it farther than normal; the jaw was

Fig. 4 (case 2).—*A*, patient sitting on chair; *B*, patient in more upright posture; *C*, feet in extreme supination; *D*, left foot relaxed

thoracic kyphosis and scoliolordosis. The head was pulled back and to the right. Choreoathetoid movements of the entire body were noticed, which were variable in excursion, amplitude and degree and were more severe when she was excited and apprehensive. The hyporeflexia was of equal degree on the two sides

In the interval since this admission the bodily deformity has increased. The patient is now agonized by the involuntary twisting of the head and the contraction of the left lumbothoracic region, which causes the left scapula to reach the pelvic crest.

Examination.—Physical examination revealed extreme increase in dorsal extension of the lumbar lordosis, with prominent kyphosis to the left in the lower dorsal region and rotation of the pelvis to the left, so that the left scapula rested on the left ilium when the patient sat up. There was angulation of the left portion of

opened wider than normal. The fully extended tongue could be bent backward on itself.

Mental and laboratory examinations revealed nothing abnormal.

The question of operation was discussed with the patient, but she stated that her symptoms were not sufficiently severe or incapacitating to justify surgical procedure.

Film Analysis.—The patient was sitting on a chair. The upper part of the trunk was bent far to the left, so that the chest and the pelvic portion formed almost a right angle (fig. 4 *A*). The head and both arms were held in a natural position. The right thigh was adducted; the left foot was kept in extreme supination, and the right foot was held in extreme pronation and lateral flexion.

Analysis of the films revealed them as alternating movements in which flexion and extension of the forearm, hand or fingers followed one another. But, unlike the regular repetition of alternating units (consisting of flexion and extension), as observed in antagonist tremor, the units of these alternating movements appeared at irregular

The symptoms consisted exclusively of this involuntary motor activity. Neurologic examination did not reveal any other abnormality. From the clinical point of view one may speak of an elective systemic disease which affects exclusively motor relaxation and the appropriate distribution of motor innervation. No cause

Fig. 2 (case 1).—Alternating flexion and extension of left hand at wrist.

intervals. In order to differentiate this form of alternating movements from antagonist tremor, it should be called "myorhythmia."

Very rapid, ticlike twitchings could be differentiated as another form of involuntary movements. Opening and closing of the hand occurred in less than half a second. These twitchings came on occasionally, at completely irregular intervals.

responsible for the development of this steadily progressive process could be determined.
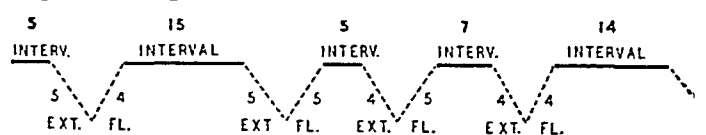
Fig. 3.—Evaluation of alternating movements in figure 2. (Note the irregular intervals [5—15—5—7—14 frames]).

After a while the tension in the left foot relaxed, and the foot returned to a middle position; meanwhile, the right foot remained in the previous position (fig. 4 C and D). At the same time, as the left foot relaxed the trunk took a more upright position (fig. 4 B). Figure 5 shows a series in which pronation of the movements of the right hand appeared (dorsal and volar flexion, with slight flexion and extension of the fingers). The intervals between the alternating units were completely irregular. Sometimes only one alternating unit appeared; sometimes bursts of three, five or more, always at different intervals. Figure 6 shows
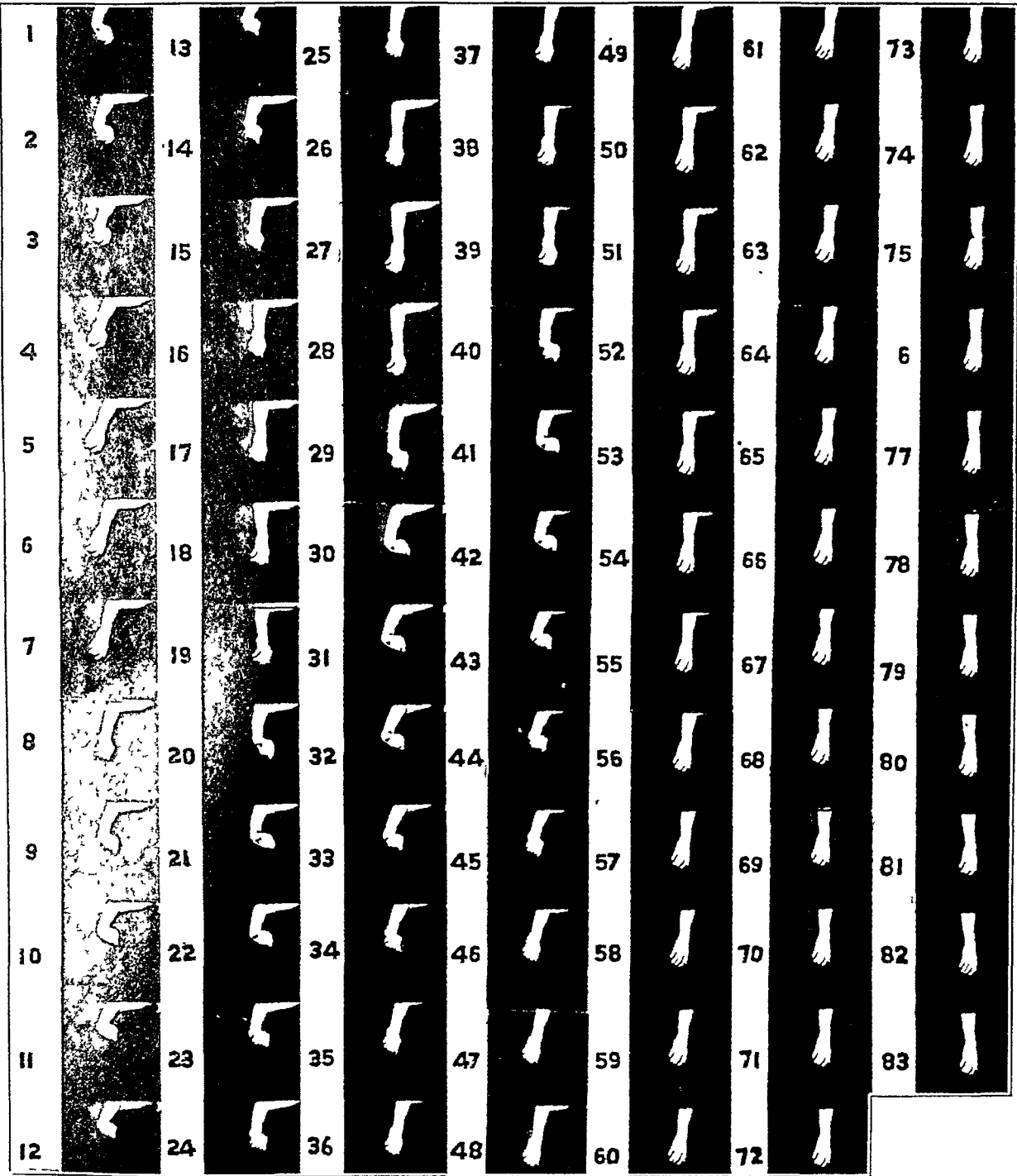
Fig. 6 (case 2).—Alternating movements of hand, with different time intervals between them.

right foot relaxed. The peculiar position of the right foot was maintained for a long time; suddenly the position changed, between frame 50 and frame 51, that is, in one-sixteenth second.

Then involuntary movements of the right arm and hand started, and transient adductions of both thighs occurred. Later the patient is shown sitting, with still more pronounced scoliosis.

A close-up view of the right arm and hand revealed that after a long period of complete rest, alternating a series of successive frames which illustrate the alternating movements and the long periods of complete rest. Sometimes the end position of an extension was maintained for a few frames before a flexion followed. Much less involuntary movement was present in the left hand.

A close-up view of the legs and feet revealed slow adductions of the thighs at irregular intervals, those on the two sides being independent of each other. The long-maintained positions of the feet were most pronounced,
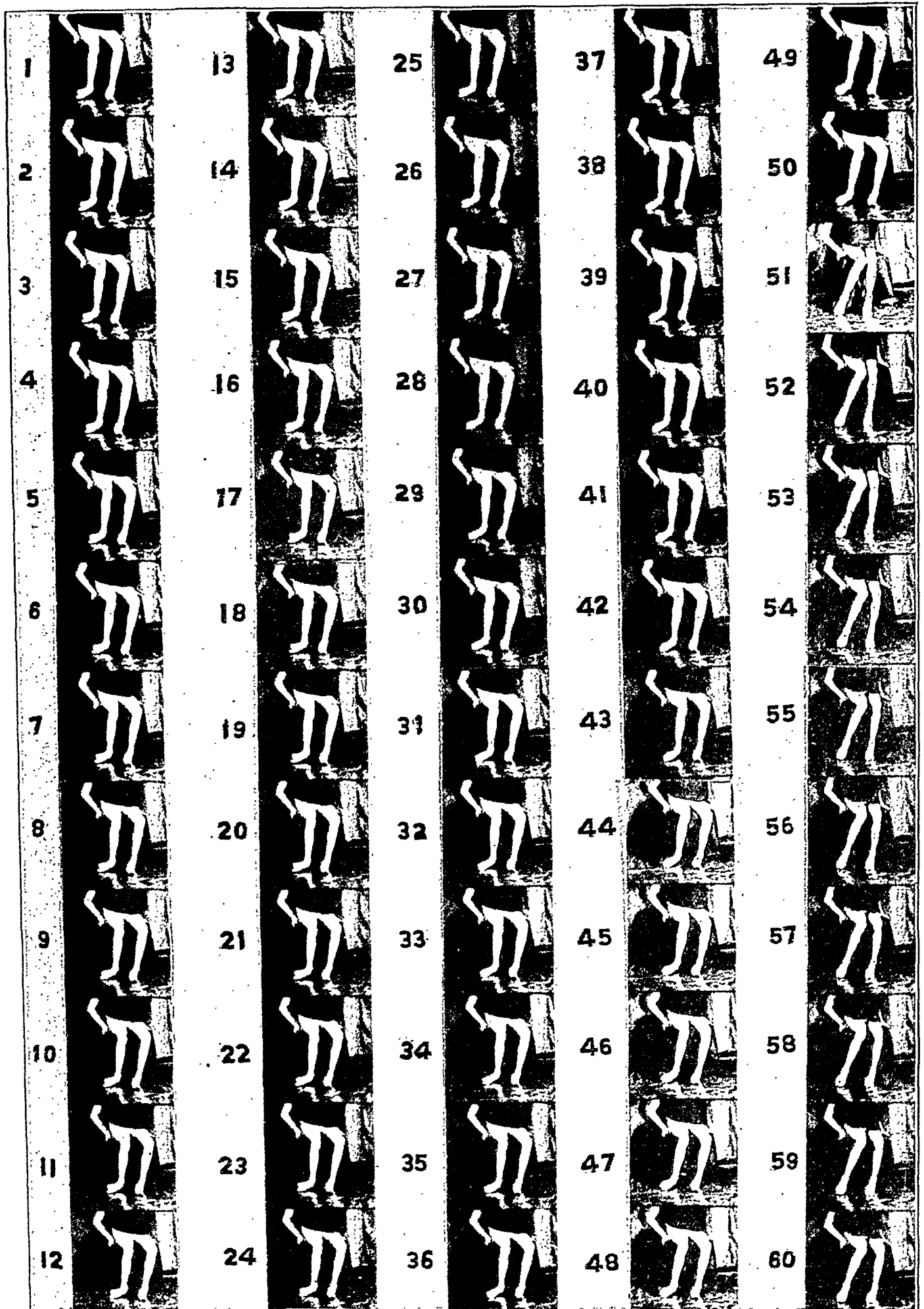
Fig. 5 (case 2).—Posture of right foot, maintained for a long time, with sudden change between frame *50* and frame *51*, that is, in one-sixteenth second.

Since the operation the patient has resumed his teaching and has felt much better. It is his subjective impression that only his "tensions," particularly those in the shoulders and neck, have been benefited, and that his involuntary movements have not been improved to the same extent.

Film Analysis.—Preoperative Pictures: When the patient was sitting (fig. 7 *A*), the head was bent far to the right and turned to the left. The right shoulder was drawn up, and the upper portion of the right arm was abducted. The trunk was twisted to the left.

When he started to raise his arms to the horizontal position, both shoulders (the right more than the left) were drawn up, and the head was bent farther to the right. While the arms were held in the horizontal

long time. After he had stood longer, the bending of the trunk increased, and the trunk turned more to the left (fig. 7 *E*).

In his walking there was some instability; the right leg was held stiff for a few steps and then lifted from the ground in wide circumductions. Suddenly the bending of the trunk increased, and sustained tensions appeared in the muscles of the neck, shoulders and back. Transient tensions bent the upper part of the body forward or to the left. There was an almost continuous overflow of balancing movements of the right arm.

When he was in the sitting position, the trunk was held fairly straight (fig. 7 *C*). There were slow, sustained movements of the muscles of the shoulder girdle
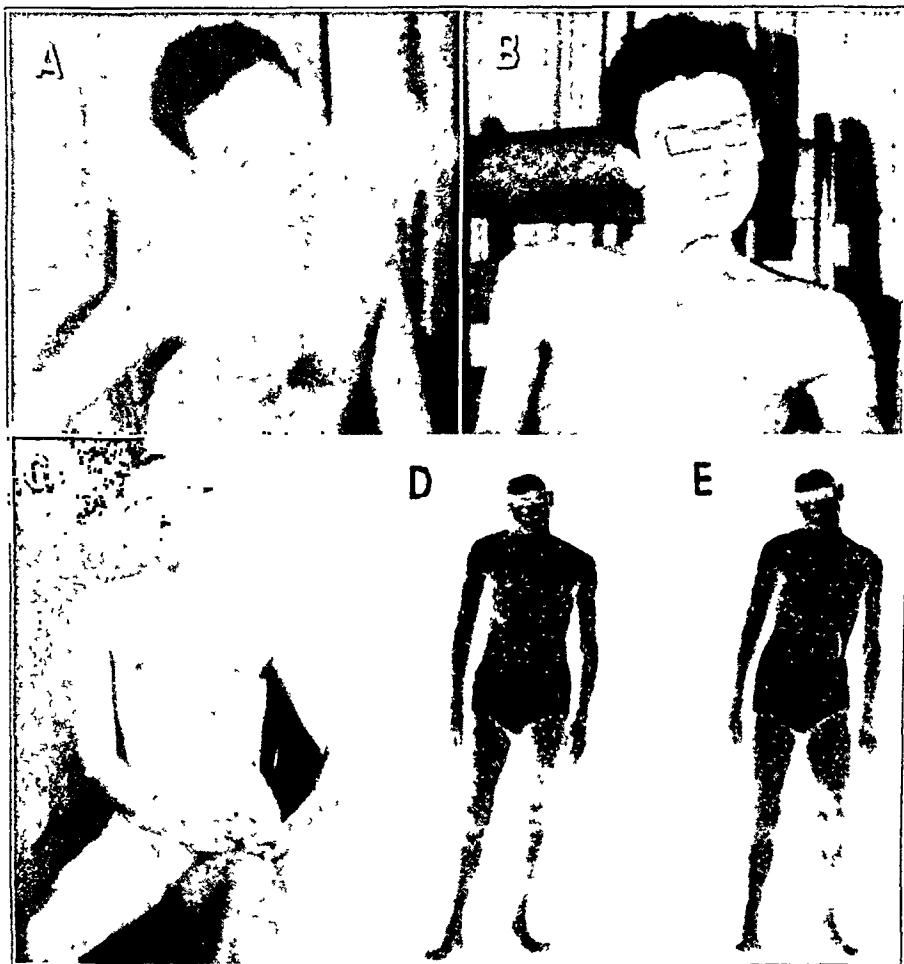
Fig. 7 (case 3).—*A*, preoperative picture; *B*, appearance of patient five weeks after operation; *C*, *D* and *E*, appearance two years after operation.

position, there were irregular, slow involuntary movements of the upper part of the arm and alternating movements of the right arm and hand. The trunk was more twisted and was bent far to the left, and the head was drawn to the left.

While he was walking, tensions of the right leg, the shoulder girdle and the trunk and wide balancing movements of the right arm appeared. These sudden tensions made the gait resemble jumping.

Postoperative Pictures (May 26, 1941): With the patient standing (fig. 7 *D* and *E*), the head was held slightly bent to the right and turned to the left. The trunk was bent to the left. The right shoulder was held higher than the left. He stood with the legs apart. The right leg was completely extended. There were some turning movements of the head. The right leg was inverted and was kept in this position for a

and the pectoral muscles. As soon as he raised both arms to the horizontal position, the curvature of the spine to the left increased, and the right shoulder was higher than the left. Irregular movements of the right arm and hand appeared, part of them of alternating type.

When the patient drank a cup of water held in the right hand, involuntary movements appeared in greater number in the right arm and shoulder. The shoulder was drawn farthur up and was kept in this position for a time. The head was bent to the right. There were sustained tensions of the muscles of the shoulder and the pectoral muscle and alternating movements of the right arm and hand. When he drank with the cup in the left hand, involuntary movements appeared almost exclusively on the right side.

the right foot being in pronation and the left in supination. This seemed to be a position of predilection of the feet; it disappeared and appeared again (fig. 4 *C*).

A close-up exposure of the head and neck showed slow contractions of the right sternocleidomastoid muscle and of the pectoral muscles, more on the right side than on the left. The head was usually bent to the left.

When the patient was standing, the kyphosis of the trunk was much less pronounced. There were abundant involuntary movements of the right hand of the same character as those already described. In walking there were extreme kyphosis and lordosis of the spine, and the whole trunk was bent forward at the hips. The left leg was more flexed at the hip than the right leg, and the left foot was in extreme plantar flexion, so that only the toes touched the floor in walking. Before the patient started to take the first step she had both soles on the floor. At the moment she lifted the left leg out, the persistent plantar flexion of the foot appeared.

A finger to nose test showed no ataxia. There was no motor disturbance in either arm when she drank a cup of water. As she lit a match some involuntary movements of the right arm appeared, but did not interfere with the act.

In passive movements both arms and hands appeared hypotonic. In passive movements of the head the sustained contractions of the right sternocleidomastoid muscle sometimes stopped the movement.

There was no history of a birth injury, and the patient's early development was normal up to the age of 8 years, when motor disturbances began. On her first and second admissions to the hospital this condition was described as deformity and rigidity, of variable intensity and degree, with dystonic tensions maintained for longer and shorter periods. The course of the disorder was steadily progressive. After the disease had been present about twelve years, the postural disorder was extreme. Some positions were maintained permanently during observation, but suddenly appearing changes and relaxation of the affected part gave evidence that sustained tensions were responsible for their appearance. More transient dystonic movements, at completely irregular intervals, appeared in the neck, the shoulder girdle and the extremities. In addition, more rapid alternating movements, with the characteristics of myorhythmia, particularly of the right arm and hand, appeared between them.

The resistance to passive movements seemed to be diminished when involuntary motor activity was not present. Only when tensions appeared in the part under examination did sudden obstruction hamper the passive movement and give the impression of increased resistance to such movements. This phenomenon has been described as alternation of hypotonia and hypertonia. But the basic condition of the muscle and its reactions to passive movements are not changed. Only the suddenly appearing sustained tensions interfere with the continuous course of the passive movement.

Except for the involuntary movements and postures, the neurologic examination did not reveal any disturbance. The outstanding clinical feature of this progressive disease is the elective systemic appearance of dystonic disorders in a healthy child. No etiologic factor could be determined.

CASE 3.—*History*.—E. S., a man aged 34, entered the hospital in 1938.

His birth was normal, as was his early development. He started to walk and talk at the normal age and entered school before the average age. He was well until the age of 12 years, when a disturbance in his right hand developed gradually. "I could not propel the pencil across the page; it seemed to me I had not enough power to guide the pencil. I had to lift my arm in the shoulder, and then this feeling disappeared." This symptom was followed soon by irregular alternating movements of the entire right arm, which occurred only when the arm was kept extended. In 1918, during the influenza epidemic (when he was 14 years old), he had a severe illness of about two weeks' duration. After his recovery he noticed irregular movements and incoordination when walking. At this time he could run much more perfectly than he could walk at a slow pace. At the age of 16 he first noticed the occurrence of involuntary movements of both legs when he had to sit quietly in a narrow seat. Although he could walk for a certain distance without much trouble, something suddenly would "click," and he would lose his coordination. At the age of 20 the incoordination of the legs became generally worse; he was weak and had to interrupt his college work for a year to rest on a farm. After his return to town his condition again grew worse, but he was able to continue college work, with interruptions. He acquired a teaching position and held it until 1935, when involuntary movements began to occur in his right shoulder and his back; these gradually became worse during the following two years. At this time tensions became more pronounced; there was stiffening of the muscles, and it was difficult to relax unless he lay down and rested his head against a solid support. He stated: "The tenseness was maintained for long periods and grew worse as the day went on. At night the tension was completely reduced only when I had been in bed for some time. Sometimes it took a few hours before I could relax sufficiently for sleep. During sleep all muscles were relaxed." His balance had been poor since the spring of 1937, and he had had to give up his activities. He was treated during this period with all kinds of drugs and with physical therapy and sedation, without more than transient relief.

The family history is noncontributory.

Examination.—Neurologic examination showed nothing abnormal except for the abnormal involuntary movements and the features to be described in the film analysis.

Operation.—Dr. Tracy Putnam performed an operation in September 1938. The anterior roots of the first to the third cervical segment were coagulated and crushed on each side. The spinal accessory nerve was similarly treated within the foramen magnum, and the anterior column of the cord was cut between the second and third segment on the right side.
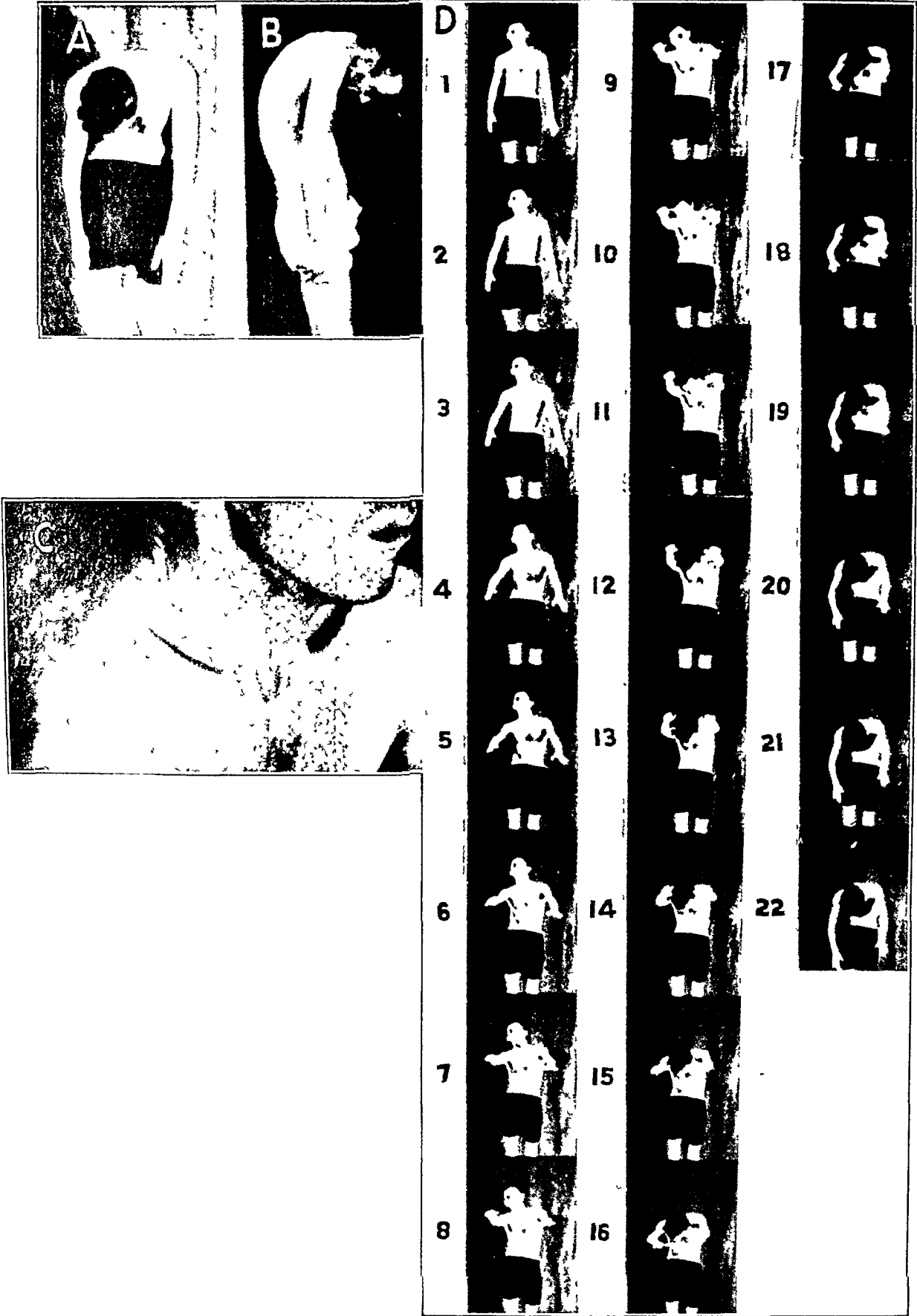
Fig. 8 (case 4).—*A* and *B*, chest bent forward and head drooping; *C*, sustained contraction of superficial and deep muscles of neck; *D*, twisting and bending of trunk as both arms are lifted to horizontal position

Writing at the blackboard with the left hand was interfered with only by tensions in the shoulder girdle. Writing with the right hand produced severe hyperkinesis: alternating movements of the forearm and hand. Sustained tensions of the whole arm sometimes stopped the act of writing. Not infrequently excessive pressure was exerted. Slow motion pictures showed clearly how the disturbances of writing were brought on.

The first symptoms developed in a normal child at the age of 12 years. Delivery and early development were without disturbance. The patient was intelligent and gave an instructive description of his symptoms, differentiating "tensions" (he used this expression spontaneously) from involuntary movements. "Tensions" were described as a feeling of stiffness in one muscle or in a muscle group which did not always lead to a movement of a limb. Sometimes it was only a "funny feeling," which came on without a recognizable reason. Sometimes he recognized that he could not carry out a voluntary act because he could not relax one part in order to move it in another direction.

The disorder started in the right arm and hand and gradually progressed to the trunk, the neck and all four extremities. During sleep all muscles were relaxed, but it took some time for complete relaxation when he was lying in bed.

The site and degree of the sustained motor activity which brought on the dystonic postures changed continuously. *D* and *E* of figure 7 show postures taken after a short interval. Analysis of the movements during this period reveals that between the first and the second position the twisting of the trunk had increased and the position of the right foot had changed considerably. Dystonic movements, not maintained nearly as long as dystonic postures, were observed in the neck, trunk, shoulder muscles and lower extremities, sometimes disturbing the equilibrium while the patient was standing or sitting. The upper extremities showed, in addition, alternating movements at irregular intervals, previously described as myorhythmia.

When voluntary movements or acts were performed, the involuntary motor activity was much increased. When the patient was walking, drinking or writing, dystonic movements and tensions appeared in greater number, and the change in posture was more extensive than when he was lying down or sitting in a relaxed position with the head and arms supported. Under these conditions the involuntary motor activity appeared as associated movements released under the influence of voluntary motor acts.

Aside from the dystonic motor disturbances, neurologic examination revealed nothing abnormal. The illness during the epidemic of influenza of 1918 came on a long time after the onset of the

motor disorder and is not of etiologic importance. One is entitled to include this case with the dystonias of unknown cause which present elective systemic symptoms and have their onset during childhood.

Comparison of *A* (fig. 7), taken before operation, with *B*, taken five weeks after operation, and *C*, taken two years after operation, demonstrates the success of the anterolateral chordotomy. The patient himself offered the observation that the improvement in the tension and the feeling of stiffness was definitely a result of the operation. The posture was much more relaxed. Although some sustained contractions appeared after operation, their extent and severity were reduced. During voluntary activity there was still some involuntary stiffening, but it did not hamper his voluntary activity as much as before operation.

CASE 4.—*History.*—N. Z., a white man aged 26, was born in Poland. There was no history of birth trauma or of familial disease. He developed properly and was in fairly good health. An attack of "sleeping sickness," at the age of 4 years, of about a month's duration, was reported, but detailed data could not be obtained.

At about 13 years of age he began to have almost constant involuntary movements of the right arm and hand. Although he was right handed, he began to use his left hand in writing. In May 1938 the patient experienced a moderate amount of dull pain in the lower lumbar region, which lasted for two days. After this he began to have involuntary movements of the muscles of the back and neck which entirely distorted his normal erect posture. He had great difficulty in walking until about a year prior to admission, when he was placed under treatment with Bulgarian belladonna root. On occasions, for about two hours after a dose of this drug, he had only slight involuntary movements.

Physical Examination.—Inspection revealed good development. There were kyphosis and scoliosis of the thoracic region, with the concavity to the right. Sustained posturing of the head, the right shoulder and the spine, with involuntary movements in the right upper extremity, was noted. Muscular strength was good on both sides; there was no atrophy. Speech was normal. The reflexes were active and equal on the two sides. The Babinski response was not elicited. Sensory examination gave normal results. The patient was cheerful, cooperative and of adequate intelligence.

Laboratory tests gave normal results. The electroencephalographic record was normal. Hyperventilation did not elicit any abnormalities.

Operation.—Laminectomy was performed, and the anterior surface of the right side of the cord, between the second and the third cervical segment, was cauterized. The patient had remarkable relief immediately after operation, but improvement decreased in the succeeding weeks.

Film Analysis.—When the patient was standing, there was only slight lordosis of the spine, and the upper part of the body was slightly bent and turned to the left. The head was held upright. After a while the chest became bent forward to an extreme degree, and the head drooped (fig. 8 *A* and *B*). With the extreme lordosis, there was increased twisting of the trunk. The

After the patient's birth by forceps, gross disturbances were not noticed, but his general physical development was remarkably slow and

Fig. 9 (case 5).—*A* and *B*, dystonic posture; *C*, swinging around of leg in walking.

mental development progressed only to that of low average intelligence. The intelligence quotient at the age of 22 was only 77.

Involuntary movements started at the age of 10 years. They first affected the right lower extremity only, but progressed quickly to the trunk, the neck and all four extremities. Speech seemed to be somewhat affected also. The abnormal involuntary motor activity consisted of slow dystonic movements. They came on at different intervals in different parts of the body in continuously varying pattern and then disappeared. Their occurrence interfered with voluntary action. Maintained postures or permanent distortions were not observed. Sudden extension of the leg caused disturbance in walking. Neurologic examination revealed no other abnormalities. Dystonic motor disorders were, again, the only elective symptom of this disease.

There was no history that a birth injury had caused a localized gross lesion in the brain. But the slow physical development and the reduction in mental growth lead to the presumption of the presence of a malformation of the brain at birth. The disease, which started at the age of 10 years, developed in an already abnormal nervous system. Whether the same process caused the developmental retardation and, after a latent interval of at least ten years, the progressive hyperkinesis, or whether a progressive process appeared at the age of 10 in a malformed brain, cannot be decided from clinical observation alone.

CASE 6.—*History.*—K. G., a single woman, entered the hospital at the age of 28. The family and the past histories were essentially noncontributory. When she was 12 years old, she noticed that her writing became unsteady and that she had difficulty in controlling the movements of her right hand. This difficulty existed for one year; she was then free from it for three years. In her third year in high school the trouble returned. It became so extreme that she was unable to hold a teacup, knife or fork. Later involuntary movements appeared, and her right arm and hand would twist and turn even when she was at rest. In 1936 the same difficulty gradually developed in her left hand. In 1941 she noticed that her head moved spontaneously and that she was unable to control its motion. Shortly thereafter a feeling of tightness developed in the back of her neck, and her head began to pull to the left. This condition persisted until her admission to the hospital, in February 1942.

Examination.—Physical examination revealed no pathologic condition of the inner organs. The heart and lungs were normal; the blood pressure was 110 systolic and 80 diastolic. Neurologic examination showed no weakness of the extremities. The tendon and the abdominal reflexes were equal and active on the two sides. No pathologic reflexes were elicited. Sensory examination gave normal results, and there was no abnormality of the cranial nerves.

The report of the psychologic examination was as follows: "The patient is a young woman of high average intelligence. She does better work with verbal material,
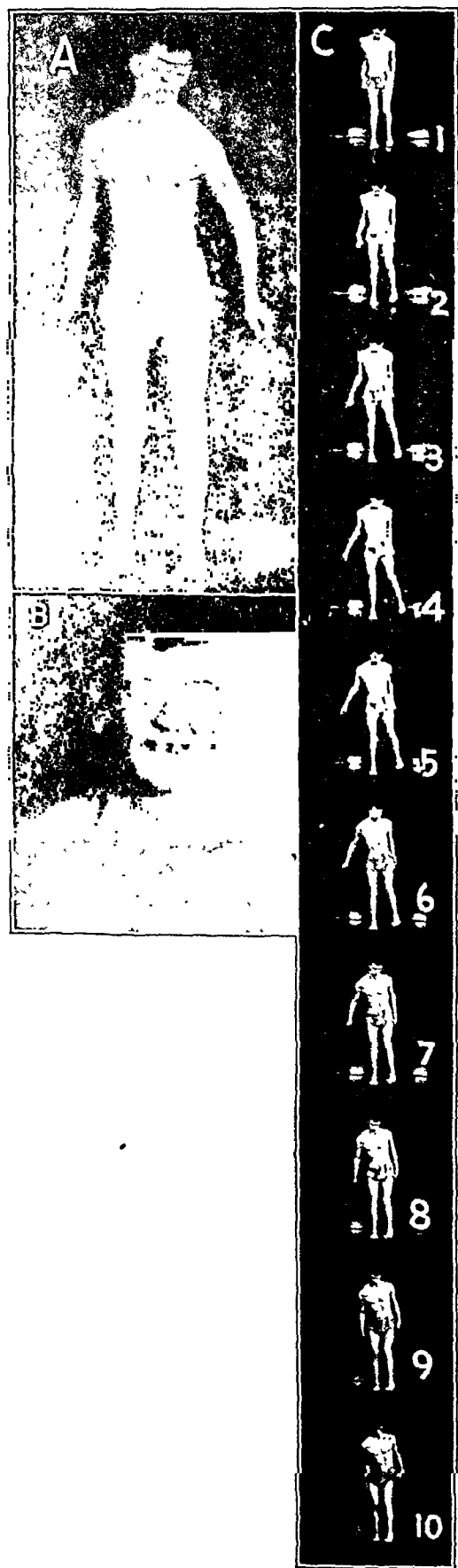
right shoulder drooped. This posture was maintained for a while; then the patient returned to the upright position. During the twisting of the trunk involuntary movements of the neck, shoulders and both arms occurred. A close-up series of the right arm showed sustained tensions, resulting in adduction and extension at the elbow, which was maintained for a while.

When the patient lifted both arms to the horizontal position (fig. 8 D) bending and twisting of the trunk were produced, so that he was forced to balance the position of the right arm continuously.

A close-up picture of the neck and shoulders showed irregular contractions of the muscles of the upper portions of the arms and the shoulder blades and the deep and superficial muscles of the neck. The contractions were long sustained and appeared and disappeared at irregular intervals. Sometimes the contractions of the trapezius and sternocleidomastoid muscles (fig. 8 C) were maintained for a few seconds. The right side of the neck and the right shoulder appeared to be more affected than the left.

Two series of motion pictures, taken four weeks and six months, respectively, after operation, revealed no change in the original position, and appearance of alterations in position and tensions was the same as before. When the patient brought the arms to the horizontal position there was, again, increase in bending and twisting of the trunk, with balancing movements, particularly of the right arm. Sustained movements of the muscles of the neck and shoulders were visible.

A boy with a history of normal delivery and development was reported to have had an attack of "sleeping sickness" at the age of 4 years. It seems doubtful whether he suffered from epidemic encephalitis at this time, for, he did not show any residuals of the disease in the following years and was healthy until the age of 13, when involuntary movements of the right arm began. Further progression occurred at the age of 24, when sustained tensions started in the muscles of the neck and back. At the age of 26 dystonic movements of the deep and superficial muscles of the neck were present, but particularly remarkable was the distribution of tensions which caused the peculiar posture. The upper part of the spine was bent forward, and the head drooped. This postural disorder predominantly occurred as an associated movement brought on by other motor activity, such as standing for a longer period or raising the arms to the horizontal position.

In addition, there were some alternating movements of the right arm, which also appeared as associated movements with voluntary movements of the upper extremities.

No other abnormalities were revealed by the neurologic examination. Specifically, oculomotor symptoms, rigidity, tremor and other possible evidence of chronic epidemic encephalitis were not noted.

Clinical observation and examination revealed only a progressive disease, without evident cause but with elective systemic symptoms, consisting of dystonic movements and posture.

The surgical procedure (anterolateral chordotomy) was without effect on the involuntary motor activity.

CASE 5.—R. A., a man aged 22, was referred to the Neurological Institute for possible operation to correct his involuntary movements, which involved all four extremities, the head and the neck. His delivery had been completed by forceps. He had been rather slow in general development. His teeth appeared at the age of 2 years; he did not begin to sit up until he was 4 and did not walk until he was 7 years of age. At the age of 10 years involuntary movements of the right lower extremity were noted. Shortly thereafter all four extremities were somewhat involved. These involuntary movements gradually progressed and reached their greatest development at about the age of 15. Since that time his condition has remained static.

The family history was noncontributory.

Physical Examination.—The patient was able to walk and seldom fell. Muscular strength was generally good, with no apparent difference on the two sides. Speech was slow, explosive and slurred. The deep tendon, abdominal and cremasteric reflexes were present and equal on the two sides. No pathologic reflexes were elicited.

Sensation and the cranial nerves were normal.

Psychometric examination revealed low average intelligence, with an intelligence quotient of 77.

Laboratory examinations revealed nothing of significance.

As the boy seemed to be fairly well adjusted, Dr. Putnam felt it was inadvisable to perform an operation, lest weakness be produced on one side and the patient further incapacitated.

Film Analysis.—When the patient was standing (fig. 9 A), the head was tilted and turned a little to the left. The trunk was also turned to the left. The left arm was held slightly abducted at the shoulder and bent at the elbow. The right arm hung down in a natural, relaxed position. The legs were held apart, and the left leg was slightly adducted and inverted. The right sternocleidomastoid muscle was in constant, clearly visible contraction (fig. 9 B). There were slow turning movements of the head to the right. Both arms swung around to the back, and at the same time there were irregular alternating movements of the upper part of the arm and the forearm. These movements were sometimes arrested by sustained tensions.

When the patient spoke, the turning movements of the head increased in number, and slow movements of the shoulder girdle appeared, with adduction of both arms.

There were little hyperkinesis of the face and only a few movements of the hands and fingers. The hands showed only movements associated with movements of the entire arm.

The finger to nose test revealed no ataxia but brought on an increase in torsions of the trunk and head to the left.

When he was walking, increase in torsions of the trunk and head and in the involuntary movements of the arms was evident, but the gait was most interfered with by long-sustained extension and adduction of the left leg. The leg swung around like a stick, and the knee was not flexed (fig. 9 C). The foot did not drop but was held in a natural position.

In walking the patient exhibited increased turning movements of the head, and the spine appeared much more bent than when she was standing. Both arms presented the usual number of associated movements.

After operation only the position of the head was improved (fig. 10 D). The head was held straight; the position of other parts of the body was unchanged. There were the same involuntary movements of the shoulder girdle, hands and fingers.

After normal delivery and normal development, the patient first showed motor disorder of the right arm and right hand at the age of 12 years. The movements were not severe and interfered only with the act of writing. After apparently complete recovery for about three years, involuntary motor activity recurred in the right upper extremity. Now the disorder was steadily progressive, and twitching and turning movements of the right arm appeared. Further progression was noticed at the age of 23, when both arms, and the neck and the trunk were affected. The face and the lower extremities never showed any involuntary motor disturbance.

At the time of observation, the most troublesome symptom was the torticollis. Besides the slow turning movements of the head, dystonic movements of the muscles of the shoulder girdle and the back appeared at irregular intervals and were maintained for various periods. Tensions of longer duration caused peculiar postures of the head (torticollis), the upper extremities and the trunk (kyphosis and lordosis). In both hands slow, athetotic, irregular movements of the fingers were intermingled with alternating movements, described previously as myorhythmia. In walking both types of involuntary activity, the dystonic symptoms and the alternating movements, were increased in intensity.

The operation was successful in relieving the torticollis. The head was maintained in a straight position, and the sustained contractions of the left sternocleidomastoid muscle were considerably decreased.

The neurologic examination did not show any abnormality except for the dystonic symptoms. Here, again, is a case with elective appearance of dystonic symptoms without a recognizable cause. Although the first symptoms appeared at the age of 12 years, the real progress of the disease began several years later. The progress was not as rapid as that when the disease had an earlier onset.

CASE 7.—*History.*—A. K., a woman aged 32, was born in New York, of Russian Jewish stock. There was no apparent hereditary tendency in the family. Delivery was normal, and her weight at birth was 12½ pounds (5,670 Gm.). Development was normal, without any disturbance. After leaving high school, at the age of 16, she worked as a stenographer. She was well up to the age of 18. At this time she noticed slight dragging of the left leg when she walked. During the first few years, in which she had this feeling alone, even physicians could see nothing peculiar in her walk. The region of the left hip and thigh was affected; in addition, she later felt "a sort of strain" in the left knee. In 1930, at the age of 24, she had increased difficulty in walking. She stated: "At this time it seemed to change the posture; I began to twist and turn in the hip, but only in walking." In addition, her handwriting became poor. In writing she felt a "tension" in the right forearm, which became more pronounced in the year preceding admission to the hospital.

At the time of admission she complained only of tension in the left leg and in the left side of the back when she was walking. Some tremor appeared in the left leg when it was under strain, e. g., when she put weight on it. In walking the foot turned inward at irregular intervals. It tired her to make the movements of walking, and she used the right leg more than the left. This difference was pronounced when she kept her arms together or when she carried packages in her arms. "It seems to lock my left leg, and I can't operate it without balancing; this is due also to the tensions in the back." She had no other physical complaint.

Physical and neurologic examinations did not reveal anything abnormal except for the motor disorder, to be described later.

Film Analysis.—When the patient stood or sat, the position of the head, trunk and upper and lower extremities was not changed. No lordosis or kyphosis was noted. When she walked, and still more when she crossed her arms over her chest in walking, slow outward rotations of the left leg appeared at irregular intervals. At the same time, contractions of the muscles of the left lower part of the back appeared, which caused slight bending of the spine to the left.

In slow motion pictures the differences between the regular movements of the right leg and the slightly distorted movements of the left leg in walking were clearly recognizable.

A healthy girl, with a history of normal delivery and normal development, had a gradual onset of motor disturbances at the age of 18 years. When she was walking, she noticed the feeling of tightness in the left lower extremity. The feeling was only subjective; numerous examiners failed to recognize any motor defect at this stage of the disease. At the age of 24, tensions appeared in the right arm and caused difficulty in writing; she then exhibited visible changes of posture in walking.

Up to the age of 36, when the patient came to the Neurological Institute, there was only slight progression of the disease. When she was standing or sitting, no involuntary movements or changes of posture could be noticed. When she was walking, turning movements of the left leg and twisting of the lumbar part of the spine came on as associated movements at irregular intervals.

During the whole course of the disease these dystonic symptoms were always the only objective sign. Neurologic examination revealed no other abnormality. No etiologic factors could be identified.

as one would expect in view of her difficulty in the use of her hands."

Roentgenograms of the skull revealed nothing abnormal.

Operation.—Operation was performed by Dr. Putnam on two occasions. At the first operation a laminectomy was performed, and the anterior roots of the first, second and third cervical spinal segments, together with the spinal accessory nerve, were crushed and cauterized bilaterally. After operation the patient felt much more relaxed, but there was still tension of the left sternocleidomastoid muscle, which produced tilting of the movements of both hands and the fingers. The spine showed lordosis and kyphosis of variable intensity, the concavity being turned to the right.

A close-up view of the upper part of the body showed intermittent, long-sustained contractions of the left sternocleidomastoid muscle and some contractions of the shoulder and the pectoral muscles, more pronounced on the left side than on the right (fig. 10 *B*).

A close-up view showed two kinds of involuntary movements of the hands and fingers: (1) slow movements at irregular intervals with a continuously changing pattern, consisting in dorsiflexion of the hand with
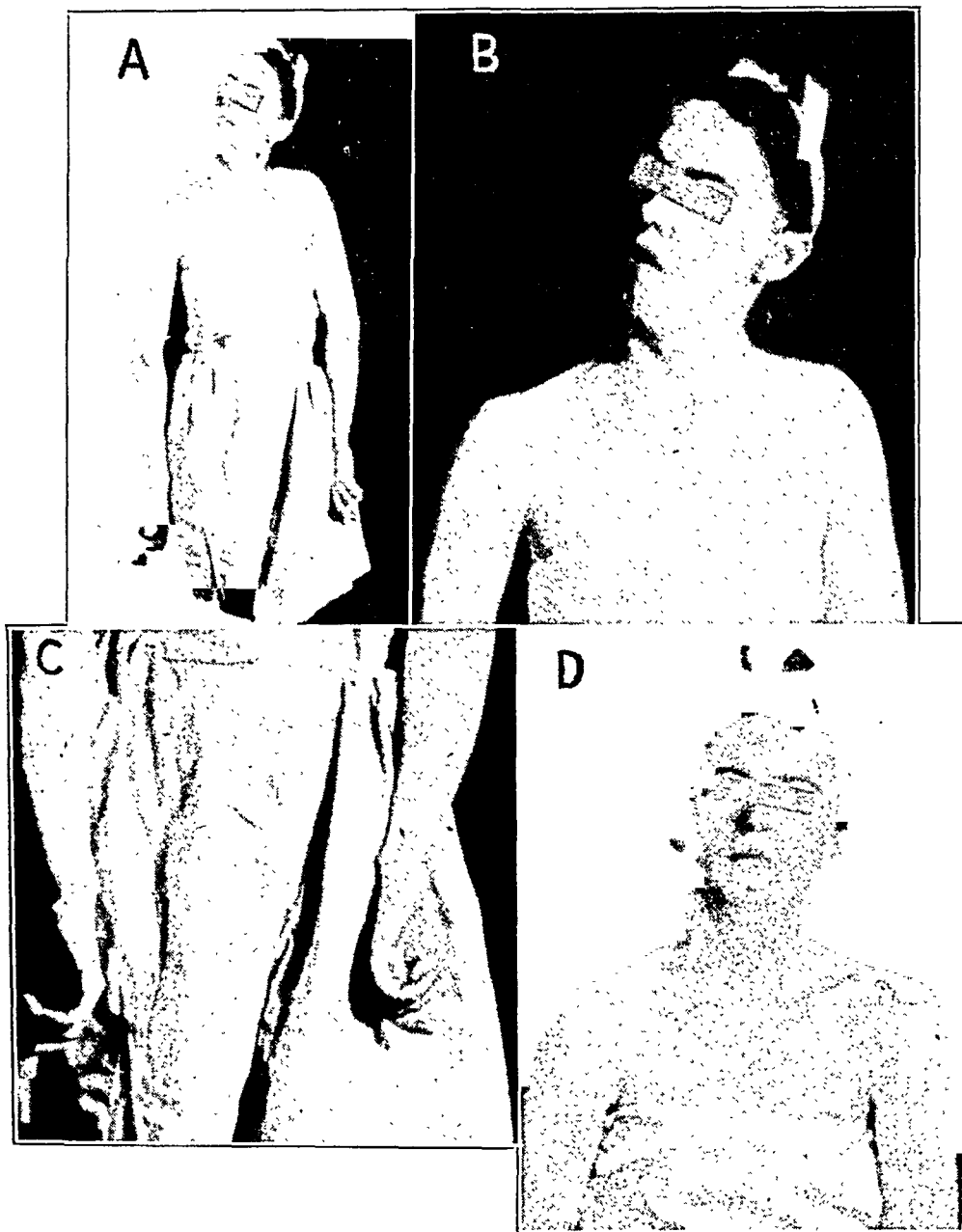
Fig. 10 (case 6).—*A, B* and *C,* preoperative pictures; *D,* postoperative picture.

head to the right. On the twenty-fourth postoperative day the left spinal accessory nerve was sectioned at the neck. After this operation the head could be held in good alinement, and there was no palpable abnormal tension of the muscles of the neck. Movements of the muscles of the arm were of the same type as before operation.

Film Analysis.—When the patient was standing the head was bent slightly to the left and turned far to the right. The trunk was bent to the right, and the left shoulder stood higher than the right. Both arms hung down and were in extreme pronation, so that the palms faced outward (fig. 10 *A* and *C*). There were turning movements of the head and involuntary extension of one finger, flexion of the thumb and another finger, radial or ulnar flexion of the whole hand and extension of the thumb, and (2) alternating movements of the hands and fingers, consisting in dorsiflexion and volar flexion of the whole hand, extension and flexion of some of the fingers, and pronation and supination of the forearm and hand. The intervals between these antagonistic units were irregular. The pattern changed frequently: Flexion and extension of the fingers were followed by pronation and supination of the hand; then radial and ulnar flexion of the hand was carried out a few times. As these two kinds of movements were intimately mingled, the pattern of hyperkinesis was complicated.

trunk was much increased. This posture was maintained as long as the arms were kept raised. After the patient lowered his arms, he assumed his original position. When he stood upright, he kept his head turned farther to the left than when he was in the sitting position. The curvature of the trunk was almost the same in the two positions. This change in posture appeared again as the patient was turning around and as he kept his hands outstretched in front (fig. 11 C).

In the second part of the film, taken four months after operation, the posture was not much changed except that the left shoulder drooped more. A close-up view of the head and chest (fig. 11 D) showed sustained tensions in the platysma muscle and in both pectoral muscles (more on the right side than on the left). At irregular intervals the muscles on the two sides contracted in complete independence of one another, and the contractions were maintained for quite different periods (fig. 11 E). During some contractions the head was drawn to the left; sometimes only the pectoral muscles contracted, without the head's being affected.

Contractions of Left Pectoral Muscle: Contractions appeared in two frames, were sustained in nine frames and disappeared in one or two frames. Again, they appeared in two frames, were sustained in thirty-seven frames and disappeared in two frames. After an interval of six frames, a new contraction appeared in two frames and was sustained for one hundred and five frames. During this sustained contraction of the left pectoral muscle, shorter contractions of the left platysma, the left trapezius and the right pectoral muscle appeared and again disappeared.

In a man who had never been ill before, dystonic contractions of the left sternocleidomastoid muscle appeared at the age of 23. Nothing is known of any disturbances during delivery or in his later development. No infectious disease or other condition could be considered as an etiologic factor. Physical examination did not reveal any abnormality except the involuntary motor activity.

There was only slight progression of the disease. At the time of observation, when the patient was 31, the sustained turning movements of the head were still present; in addition, contractions of the pectoral muscles were long sustained, and contraction of the muscles on one side of the back produced changes of posture. These postural disorders came on spontaneously but appeared more regularly when the patient made voluntary movements with his arms or was walking.

The predominant symptom in this case was the torticollis, but in the progression of the disorder from the muscles of the neck to the pectoral muscles and the muscles of the back the condition resembles the picture in cases of the dystonia group. The combination of late onset with slow progression and circumscribed distribution of systemic motor symptoms is notable.

The patient felt subjectively better after the operation and has returned to work.

CASE 9.—*History.*—P. W., a white boy aged 9 years, entered the hospital for an anterolateral chordotomy.

The history revealed that the mother's pregnancy was normal and that after a precipitate delivery, the infant was cyanotic and required artificial respiration. His weight at birth was 4 pounds 4 ounces (1,928 Gm.) and later fell to 3 pounds 7 ounces (1,559 Gm.). At the age of 3 months the child did not move his limbs like a normal child. General weakness was noted in all extremities. During the following years the child was bedridden, requiring constant nursing attention. At the age of 6 years tendon-lengthening operations were instituted. They partially relieved the severe pain, but it was necessary to keep the patient under the influence of phenobarbital. During the last few years the vertebral column had become more curved, and the child had been subject to attacks of stiffness of all the extremities, especially on the left side. These usually consisted of sudden extensions of the extremities, accompanied by muscular pain. Passive flexion by other persons relieved the pain to some extent. The patient's general intelligence was good.

The family history was noncontributory.

Examination.—The patient was poorly nourished and had numerous deformities of the body, including pronounced lumbar kyphosis and lordosis, with the convexity to the right, and asymmetry of the thorax, the subcostal margin and the iliac crest on the left side approaching one another. The right thigh was abducted to an angle of 75 degrees; the right foot was dorsiflexed; the left thigh was rotated internally, with dorsiflexion of the foot to an angle of 80 degrees; the left arm was abducted to 90 degrees, with flexion at the elbow, wrist and fingers, and the right arm was held at the side and flexed at the elbow, wrist and fingers. He could not walk, sit erect or hold up his head. When he was on his back, there were episodes of tonic contractions, during which he went into opisthotonos; this occurred about every five minutes and lasted about a minute. These spasms appeared to be extremely painful. Muscular development was poor throughout. Speech was slurred. The reflexes were hypotonic.

Nothing abnormal could be found on neurologic examination.

Mental examination revealed a normally bright child.

Laboratory examinations showed nothing abnormal.

Operation.—The left anterolateral aspect of the cord, above and below the fourth cervical nerve root, was cauterized. Since then the patient has been able to rest comfortably in bed and sit up in a wheel chair.

Film Analysis.—Preoperative Series: The patient was lying on a stretcher (fig. 12 D), with the head turned to the left. There were extreme lordosis and kyphoscoliosis, and the upper part of the trunk was twisted to the left. The left arm was flexed and pronated at the elbow; the hand was flexed, and the fingers were tightly closed. The left leg was extended and lay on the stretcher; the right leg was extremely flexed at the hip and extended at the knee. The right foot was slightly dorsiflexed; the left foot was inverted and dorsiflexed. The right arm was kept over the head and appeared loose and without tension.

In this peculiar position the body rested only on the left shoulder and the left heel, and the patient had to be supported by the nurse in order to prevent him from falling down.

The position did not change for a while. Then the left foot went into inversion, and its dorsiflexion was increased. The extended left leg made slow swaying movements, but the extreme extension was not changed

The coincidence of the late onset of the first symptoms and the slow progression and circumscribed distribution of the disorder is remarkable.

- CASE 8.—*History.*—J. F., a man aged 31, complained chiefly of torticollis, which pulled the head to the right and had been present about eight years. It began as stiffness of the left sternocleidomastoid muscle and gradually emerged into a spasm, during which the head was drawn to the right. During the first year after the onset of symptoms there was gradual progression of the disease; afterward the condition became fairly well

ankles and knees but left no sequelae. He had had no other serious illness.

Examination.—The patient was tall and well developed, with dorsal scoliosis and pronounced torticollis. The results of neurologic examination were normal except that the reflexes were slightly greater on the right side than on the left.

Operation.—Laminectomy and section of the motor roots of the second and third cervical nerves and the roots of the spinal portion of the left accessory nerve were performed by Dr. Putnam.

Fig. 11 (case 8).—*A,* patient sitting; *B,* change in posture produced by patient's raising the arm; *C,* similar change produced by patient's turning around, with his hands outstretched in front; *D* and *E,* maintained contraction of left platysma and pectoralis muscles.

stabilized. In fact, since 1932 the jerking of the head had been practically constant. The condition became worse when the patient was tired and improved with rest. Emotional upsets accentuated the disorder. Soon after the development of the torticollis it was noticed that the patient had a curvature of the dorsal portion of the spine, with the convexity to the right, and that this produced a prominence of the right side of the chest. Movements occasionally occurred in the muscles of the back.

The past history revealed that the patient had "rheumatism" at the age of 13 years, which affected the

Film Analysis.—Moving pictures were not taken before operation. The first part of the film was taken eighteen days after operation.

When the patient was sitting comfortably on a chair (fig. 11 *A*), the head was slightly bent to the right and twisted with the chin to the left. The left shoulder was kept a little lower than the right. There was slight curving of the trunk, with the concavity to the left.

Voluntary elevation of the arms to the horizontal position (fig. 11 *B*) was accompanied by change in the posture of the head and trunk. The head was extended and turned farther to the left; the curvature of the

When the boy was hanging in the arms of the nurse (fig. 12 *H*), the left leg hung loose and showed no tension, and the right leg was again flexed at the hip and extended at the knee. Again there occurred slight swinging movements of the extended right leg, with inversion and dorsiflexion of the right foot, but there were no movements of the left lower extremity.

Photographs of the back show that lordosis and kyphoscoliosis were notably reduced but that the sustained tensions of the right lower extremity continued. (These were later largely relieved by a chordotomy on the right side.)

At birth, after a precipitate delivery, the child was underdeveloped, small and cyanotic. Motor disturbances, which were noticed shortly after birth, rapidly progressed to changes of posture. Tendon-lengthening operations had to be carried out at the age of 6 years. The disease rapidly progressed during the following three years, until a pitiable condition resulted.

At the time of observation, when the patient was 9 years old, peculiar postural distortions were the predominant symptom. Some of the positions were maintained continuously, even during sleep. They were partly due to changes in bones and shortening of tendons and muscles. In addition, dystonic movements appeared, caused transitory changes in the position of different parts of the body and were maintained for various periods. The disorder was widespread; only the face was completely spared. The hands and fingers showed slight involuntary movements, which were best characterized as athetotic. The trunk and the proximal parts of the extremities were most affected by the postural distortions and slow, sustained movements.

No other neurologic abnormalities were present. The involuntary motor activity, in the form of dystonic movements and postures, was the sole symptom. From the clinical viewpoint the condition in this case was, again, an elective systemic disease.

Notable in this case was the early onset of the motor disorders. They were noticed shortly after birth, as soon as it was possible to form an opinion about motor abilities. The newborn child was underweight and underdeveloped in total function, but no gross signs of a localized birth injury of the brain were evident. Outstanding were the rapid progression of the disturbances and the wide distribution of the tension and the postural disorders.

In the case of such an advanced condition, in which permanent contractures have been formed, only partial relief can be expected from a surgical procedure. The decrease of tension on the side of operation (left) was clearly recognizable. The curvature of the spine was somewhat reduced, and the left leg showed less dystonic tensions than the right. The subjective condition

of the patient was much improved. The sustained tension had caused strange feelings, which were described as pain. After operation the intensity of these feelings was remarkably decreased.

CASE 10.—*History.*—M. B., a youth aged 18, who was referred by Dr. Leo Davidoff, was admitted with a history of motor difficulties since early childhood. He was born after a normal, full term pregnancy, which was terminated by instrumental delivery. Immediately after birth he had several convulsions, which recurred for several days, but had never appeared since. Early development was slow, and he did not begin to walk until he was 2½ years of age. Then he had difficulty in walking because his gait was stiff. This stiffness became more pronounced when he was excited or nervous, but he was able to play ball and get around fairly well. In 1931 section of the obturator muscle was done on both sides in order to correct the difficulty. This operation made it possible for him to walk on the entire foot, instead of on the toes only. Shortly before the operation the patient noticed that he was having movements of the extremities, and since the operation these movements had become constantly worse.
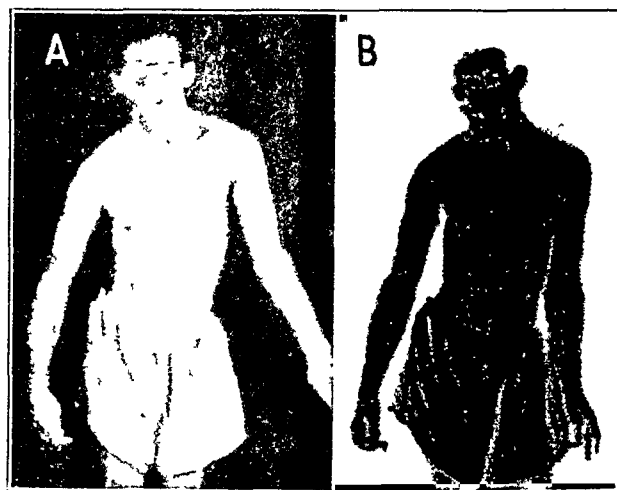
Fig. 13 (case 10).—Dystonic posture and movements.

They involved all parts of the body, including the face, tongue and neck. He stuttered when talking too fast, and the words came forth in an explosive manner. When he was relaxed the patient could write, play ball or read the paper aloud to members of his family. The patient felt that when he was relaxed the movements completely disappeared.

Examination.—The musculature was well developed, but there were thoracolumbar scoliosis and a scissors gait. Strength was generally good. Speech was explosive, with pronounced stammering and stuttering and an element of dysarthria. The reflexes could not be tested because of the tense state and involuntary movements. The right pupil was greater than the left, and the reactions were normal. The mental status was normal.

Laboratory examinations revealed nothing abnormal.

Operation.—The anterior half of the left lateral column of the cord was cauterized at the level of the second cervical segment, through a laminectomy opening, on Oct. 21, 1941. The patient was discharged, with improvement in gait and remarkable reduction in involuntary movements of the extremities of the left side.

Film Analysis.—When the patient was standing (fig. 13 *A* and *B*), the trunk was slightly bent and turned to

After a while rotation of the head and lordosis were increased. Decrease and increase in tension of the muscles of the back appeared and disappeared at irregular intervals. Suddenly the right leg was flexed at the knee (fig. 12 E), but the flexion at the hip persisted; the right leg was kept for a long time in this position—flexed hip and flexed knee. Then another extension of the lower part of the leg began and was completed in four frames. Simultaneously, extreme in-

A photograph of the back of the patient (fig. 12 B) shows the extreme lordosis and kyphoscoliosis. The child, lying on his stomach, held the left leg extended, while the right leg was flexed at the hip.

While the child was hanging supported around the chest in the arms of the nurse (fig. 12 A), the deformity of the spine and trunk was again evident, and both legs were in extreme extension. Suddenly the extended right leg was flexed at the hip. Later, slow, sustained
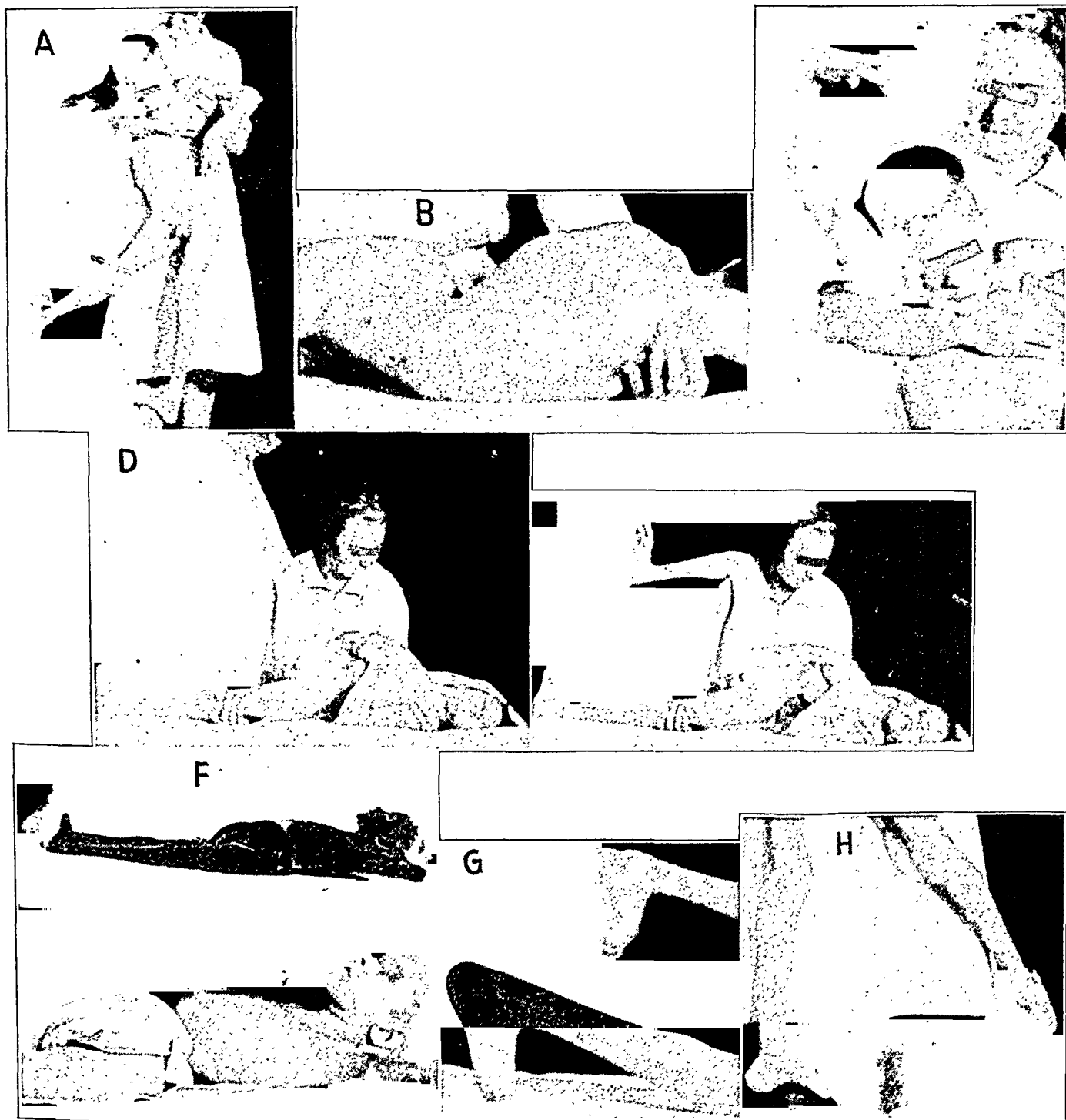
Fig. 12 (case 9).—*A, B. C, D* and *E,* preoperative pictures; *F. G* and *H,* postoperative pictures.

version and dorsiflexion of the right foot and dorsiflexion of the big toe occurred, and the lordosis and twisting of the trunk increased. This position was maintained for the next few seconds; only slow swinging movements of the right leg were observed.

Close-up pictures showed no hyperkinesis of the face. There were some alternating movements of the left forearm, the right leg and the left leg and foot at irregular intervals. Inversion and dorsiflexion of the left foot were increased and decreased at irregular intervals.

athetotic movements of the right hand and fingers were observed on the same side (fig. 12 C). Hyperextension of the right leg was maintained for several minutes, i. e., for the whole run of the film.

Postoperative Series: The patient was lying on the stretcher in a much more comfortable position (fig. 12 F). Some lordosis was still present, but was far less extreme than before operation. There was no evidence of tension, change of position or involuntary movements except for athetotic movements of the left foot (fig. 12 G).

There were no pathologic reflexes. Examination of the cranial nerves revealed no abnormalities.

Laboratory studies revealed nothing significant.

Operation.—After a cervical laminectomy, the ventral roots of the second and third cervical nerves were crushed on both sides; the spinal accessory roots were cut bilaterally, and a ventral chordotomy was performed on the right side.

Film Analysis.—The patient was sitting, or rather lying, on his chair, with high arm supports and supports for the head and feet (fig. 14 *A*).

During the observation the head was turned to the right, and the trunk, particularly the upper part, was twisted to the right. At irregular intervals sustained tensions appeared in the upper and lower extremities. They brought on changes in position of the whole arm, forearm, hand, thigh, leg or foot of irregularly changing patterns. In addition, there were turning movements of the head. It was easy to see when the tensions relaxed and the affected part became loose again. There were slow movements of the hands and fingers but no involuntary movements of the face.

Fig. 14 (case 11).—*A, B, C* and *D,* preoperative pictures; *E,* postoperative picture.

The trunk was extremely distorted. The upper part was bent to the left at an acute angle. The lower part and the pelvic portion were twisted around to the left. The head was extended. The upper portion of the right arm rested on the arm support, and the forearm was extremely flexed at the elbow and extremely pronated. Each of the fingers was in a different position, being either flexed or hyperextended. The left arm was also fully flexed at the elbow, and the upper part of the arm was pressed against the chest. The hand and fingers on the left side were held in a fashion similar to that on the right. The lower extremities were flexed at the hips and knees, and both were extremely adducted, so that the two thighs crossed. The left foot was plantar flexed and supinated.

When the patient was lying on the floor (fig. 14 *B* and *C*), the extreme distortion of the trunk was again visible; in addition, the tremendous lordosis could be seen. Otherwise, the posture was almost the same as that already described.

Suddenly a burst of involuntary movements appeared, with long-sustained turning of the head to the right and flexion of the forearms at the elbow. Then the right arm was adducted at the shoulder, and the left arm was lifted in front, with flexed elbow, and kept in this position for some time. The forearm was then extended and later flexed. Then followed a transient increase in the distorted position of the trunk.

A close-up series of the head and neck (fig. 14 *D*) showed long-sustained contraction of the left sterno-

the left. The head was turned to the right. There was severe hyperkinesis of the trunk, shoulders and both upper extremities, consisting of the following components:

(1) slow, irregular movements at irregular intervals with continuously changing pattern, the trunk and the proximal parts of the extremities being involved more than the hands and fingers, and

(2) quicker, alternating movements at irregular intervals with uniform pattern.

Slow motion pictures revealed the irregularities of sequence and pattern and showed clearly that the long-sustained movements of the trunk and the proximal parts of the extremities were more frequent than the athetoid movements of the hands and fingers.

Analysis elicited, for example, the following pattern: twisting of the trunk, turning of the head to the right, abduction of the left arm, dorsiflexion of the left hand and extension of the left index finger. Then the extended left arm was brought forward in a circle and held for a while in an elevated, extended position. Then the left arm as a whole was swung backward, and, at the same time, the left shoulder was elevated and the right arm extroverted and adducted.

The alternating movements were quick and unsustained and followed one another at irregular intervals. Close-up and slow motion pictures of the head and shoulders showed alternating raising and drooping of the shoulder girdle with interposed turning movements of the head to the left.

A close-up picture of the arms and hands showed that the throwing movements of the whole arm were more frequent than the slow, sustained movements of the hand and fingers.

When the patient was walking the disorder of posture was increased. The trunk was turned and bent farther to the left. Gait was much interfered with by the involuntary movements and by sudden, long-sustained tensions of the adductor muscles and sustained rotation of the right leg.

Four Weeks After Chordotomy.—The quick alternating movements of the shoulder girdle and the arms were not much influenced, but the slow, sustained movements and tensions of the trunk and the upper extremities were visibly reduced on both sides.

There was no paresis of the upper or lower extremities on either side. In walking the patient still showed the swinging movements of both arms. The right leg showed some adduction and inward rotation, whereas the left lower extremity was much looser than before.

In this case the boy had several convulsions immediately after delivery; these seizures had never recurred. Muscular tensions of changing intensity, which were noticed shortly after birth, produced impairment of motor abilities. Long-sustained abnormal positions of the lower extremities made walking difficult. A tenotomy was carried out because of the tension. At the age of 8 years alternating movements appeared, in addition to the dystonic symptoms. The condition progressed slowly but continuously. At the time of observation, when the patient was 18 years of age, dystonic movements of the muscles of the neck, shoulder girdles and back were pronounced. Longer-sustained contractions appeared at irregular intervals in the trunk and caused postural disorders, whereas sustained tensions of the adductor and extensor groups of the lower extremities severely interfered with the act of walking. Sometimes, when the tension came on in both adductor groups simultaneously, a gait similar to the so-called scissors gait, characteristic of bilateral pyramidal lesions, resulted. But bilateral dystonic tensions can be differentiated from stiffness caused by spasticity. Dystonic tensions come on at irregular intervals; they are maintained for various periods, and periods of relaxation—sometimes of long duration—were seen between them. Analysis of the film showed alternating movements (myorhythmia), in addition to the dystonic movements. No other abnormalities were revealed by the neurologic examination. The symptoms, again, were confined to the appearance of involuntary motor activity.

From the clinical data available, it must be assumed that a disorder of the brain was present at birth. Significant are the elective symptoms, confined to involuntary motor activity, and the mild course, with relatively slight progression up to the age of 18 years.

The anterolateral chordotomy on the left side brought about remarkable reduction of tension on the side of operation, whereas the alternating movements persisted unchanged.

CASE 11.—*History.*—G. S., a white youth aged 20, was admitted to the hospital in February 1940, complaining of generalized movements of the arms and legs.

The family history was essentially noncontributory. Birth was normal, at the end of an eight months' pregnancy. At the age of 1 month the patient was unable to suck his right thumb as he had done before and his right arm tended to straighten out and move backward. These symptoms increased in severity, and wormlike movements, first of the right arm, later of the left arm and then of both legs, gradually appeared. These writhing movements had increased in severity over a period of twenty years, but they had become definitely worse since the age of 5 years, when the patient had the first of a series of convulsions. The seizures recurred at the ages of 9 and 14, each period being about six months. During the convulsive seizures the patient's arms and legs went into extreme extension, and the neck and back were extended forcibly in the form of opisthotonos.

Ever since the onset of the involuntary movements the right side had been more affected than the left. The patient had been unable to help himself in any way since the age of 5 years and had spent the greater part of his time in a specially constructed chair, with a strap across his abdomen, his right arm doubled up behind his back and his head and neck turned to the right.

Examination.—There were pronounced cervical, thoracic and lumbar scoliosis, with a definite deformity of the thorax, and generalized muscular atrophy, greater on the right side than on the left. The patient was unable to grip well with either hand, although the grip of the left hand was slightly stronger than that of the right. The reflexes appeared equal and normal in the arms and slightly increased in the lower extremities.

crushed, and a ventral chordotomy was performed with cautery on the right side.

At the time the patient was discharged, the neurologic status resembled that on admission except that the jerking movements of the head had disappeared and the right hand was more relaxed.

Film Analysis.—When the patient was standing (fig. 15 *A*), the head was turned to the right and bent to the left. The left shoulder stood higher than the right. The left arm was adducted and slightly flexed at the elbow. The left hand was closed. There was kyphoscoliosis, with arching of the spine to the right. The right arm hung in a natural position. The legs were held apart.

A close-up series of the head showed the typical position of torticollis (fig. 15 *B*). There were some irregular

muscles of the shoulder blade was visible, without motion of the arm.

Close-up and slow motion pictures of the extended left forearm showed irregular, alternating movements of the hand at the wrist joint and of the individual fingers and the thumb. The intervals between the alternating units varied, and the pattern changed continuously. When one concentrated on the movements of the index finger exclusively, it was possible to make out flexion and extension, adduction and abduction, following each other in rather irregular sequence. The thumb made alternating movements, changing from one direction to another. Sometimes the end position of a movement of extension or adduction was maintained for a time. Various positions of the individual fingers were also
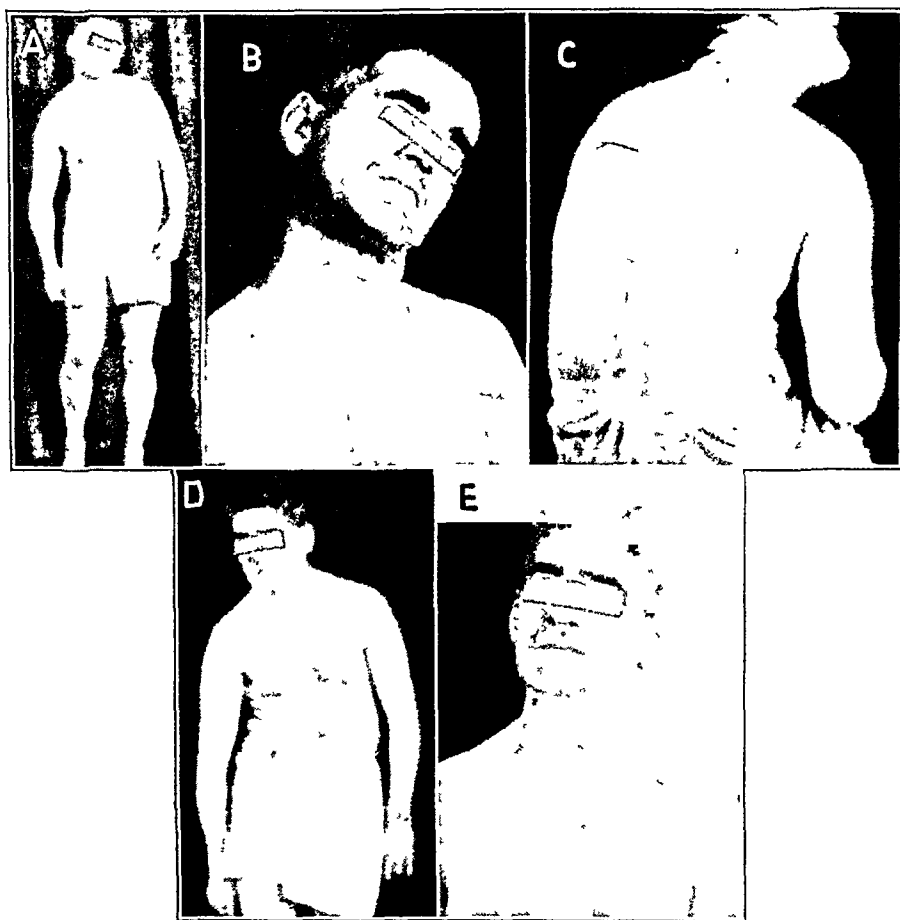
Fig. 15 (case 12).—*A, B* and *C*, preoperative pictures; *D* and *E*, postoperative pictures.

contractions of the sternocleidomastoid muscle and the deep muscles of the neck, particularly on the right side.

In walking the patient exhibited more pronounced change of posture; the head was more twisted to the right, and the scoliosis was intermittently increased, reverting to the former degree at irregular intervals. Sometimes the flexion of the left elbow was increased, and the end position was maintained for a few seconds before the tension relaxed.

A close-up photograph of the back (fig. 15 C) showed extreme lordosis, especially of the thoracic portion of the spine, kyphoscoliosis and torticollis. There were slow, irregular, sustained contractions of the muscles of the back at irregular intervals, in addition to continuous contraction of the right erector muscle of the trunk. These contractions resulted in irregular movements of the whole arm, but sometimes only the contraction of the

maintained at times, with arrest of the alternating movements.

During certain acts, such as lighting a cigaret or drinking a cup of water, the hyperkinesis was greatly increased. Slow, sustained movements of the head, shoulders and arms occurred, in addition to alternating movements of the hands, forearms and right leg. The act was seriously interfered with by these involuntary movements and tensions. For instance, a paper cup was compressed by sustained flexion of the fingers as it was being brought to the mouth, and the water was spilled. In slow motion pictures one could clearly see the different involuntary movements which were brought on by voluntary action—in the shoulders and upper part of the arm more than in the forearm, hand and fingers. It was striking that the spontaneous hyperkinesis of the left side was mild. But voluntary acts caused involun-

cleidomastoid muscle and slow contractions of the deeper cervical and pectoral muscles, particularly on the left side. The head was held turned far to the right.

There was strong resistance to passive movements of the upper and lower extremities only as long as the tensions were present. Then, suddenly, the resistance disappeared completely and passive movements could be carried out easily. Such periods of relaxation were observed at the elbows, wrists and ankle joints. They were rarely noticeable at the hips.

Four Weeks After Operation: The patient was sitting on his chair in a much more relaxed position than before operation (fig. 14 E). The head rested on the left shoulder; there was still extreme lordosis, and the trunk was twisted to the right. The legs were not crossed. No tension or particular position was noticeable in either the upper or the lower extremities. Suddenly, the right arm slipped down from the arm support and hung waving loosely, like a pendulum. There were many more involuntary movements of the hands and the fingers of the right hand than before operation.

A close-up of the head and neck showed that the muscles of the neck were completely relaxed. Passive movements of the right arm showed no tensions. Movements in the shoulder, elbow and wrist were loose.

This boy was born after a pregnancy of eight months; delivery was normal, and he did not show any abnormalities in the first weeks of life. But at the age of 1 month abnormal motor activity of the right arm was noticed. The hyperkinesis gradually increased in severity and spread over the whole body. There certainly was a continuous progression of the motor symptoms, but a remarkable aggravation of the disorder set in at the age of 5 years, after a series of convulsions. The seizures recurred twice at the age of 9 and 14 years, and have not appeared since.

During observation, when the patient was 20 years old, dystonic movements of the neck, shoulders, back and all four extremities came on in continuously changing pattern and with varying intensity. Transient postural distortions were maintained for various periods, in addition to permanent postural changes, especially of the trunk and the proximal parts of the extremities. A pitiable condition resulted, in which almost all voluntary motor activity was frustrated.

No other significant abnormalities were revealed by the neurologic examination. The general muscular atrophy was certainly due to disuse. Its distribution and the accompanying signs and symptoms, such as the state of the reflexes, did not suggest a neurogenic disorder.

There may be doubt as to whether the motor activity in the first weeks of life was really normal. In any case, it must be assumed that a disorder of the brain was present at birth. The elective systemic motor symptoms produced by this process progressed rapidly. Remarkable in this case, with the early onset of dystonic symptoms, was the occurrence of a series of convulsions. From the description, they consisted of epileptic seizures of predominantly tonic character, and not of a transient increase in dystonic tensions. Such epileptic attacks are rare in cases of systemic disease with involuntary movements. Epileptic attacks are infrequently associated with either degenerative diseases or inflammatory processes, such as chronic epidemic encephalitis, but they occur occasionally (case 46 of Herz). They may have been brought on in this case by a sudden, particularly severe progression of the pathologic process in the brain.

The operative procedure aimed at relief of the torticollis was successful. The anterolateral chordotomy brought considerable reduction of tension on the side of operation. The right arm was loose and pendulous, but, simultaneous with the reduction of long-sustained contractions, many more involuntary movements were seen in the distal parts (hands and fingers) after operation. The effect of the operation has been considerably enhanced by subsequent muscle training.

CASE 12.—*History.*—G. K., a white man aged 43, referred by Dr. Samuel Brock, was admitted to the hospital in April 1940. His birth is said to have been difficult, delivery requiring forceps, but his early development was alleged to be normal. At the age of 2 years he had an acute febrile illness in which he was comatose for forty-eight hours; no further information about this illness was available. It was noticed that at the age of 4 years he kept his left index finger extended and his thumb flexed, and at about the same time he began to display mild tremor of the left hand. About a year later he began to carry his left arm flexed at the elbow and adducted over the chest. This complaint persisted. At the age of 6 his gait became somewhat jerky, with dragging of the right foot. Since the age of 14 his right lower extremity had frequently become flexed and adducted at the hip and flexed at the knee. The foot assumed an equinovarus position, with the toes resting on the floor. Since the age of 12 or 14 he had been troubled by jerking movements of the right shoulder, which interfered with the use of his right hand. At the age of 17 he had a sudden onset of wryneck and jerking of the head, the face looking to the right. In 1931, after a disappointment, the patient had an episode of unconsciousness, and since then the disturbances in his right extremities had been more noticeable. Alcohol and barbiturates produced some improvement in his symptoms.

Examination.—The right side of the face was larger than the left. There was scoliosis of the spine, with the concavity to the left. The gait was stiff, with the feet somewhat supinated and inverted. There was moderate spasticity of the extremities on the left side, but muscle power was good bilaterally, strength being slightly better on the right side than on the left. The tendon reflexes were fairly brisk, with slightly greater prominence in the left lower extremity, and a spontaneous Babinski sign was present bilaterally. The cranial nerves were normal.

The level of intelligence was apparently high.

Laboratory studies revealed nothing abnormal.

Operation.—A high cervical laminectomy was done, and the upper three anterior cervical roots were sectioned bilaterally. The spinal accessory nerves were

cortex. No change in the movements was produced until the drug was injected into the summit of the precentral gyrus, near the midline, when palsy of the left arm appeared and the involuntary movements ceased. About 3 Gm. of tissue was excised. After an uneventful postoperative course, the patient manifested slight voluntary

was slightly turned to the left and flexed; the head was hyperextended, and the body rested on the right leg. The left leg touched the ground only with the tips of the toes. The left arm was extremely adducted, there being slight flexion at the elbow. The hand and fingers were fully flexed. The right arm was freely movable
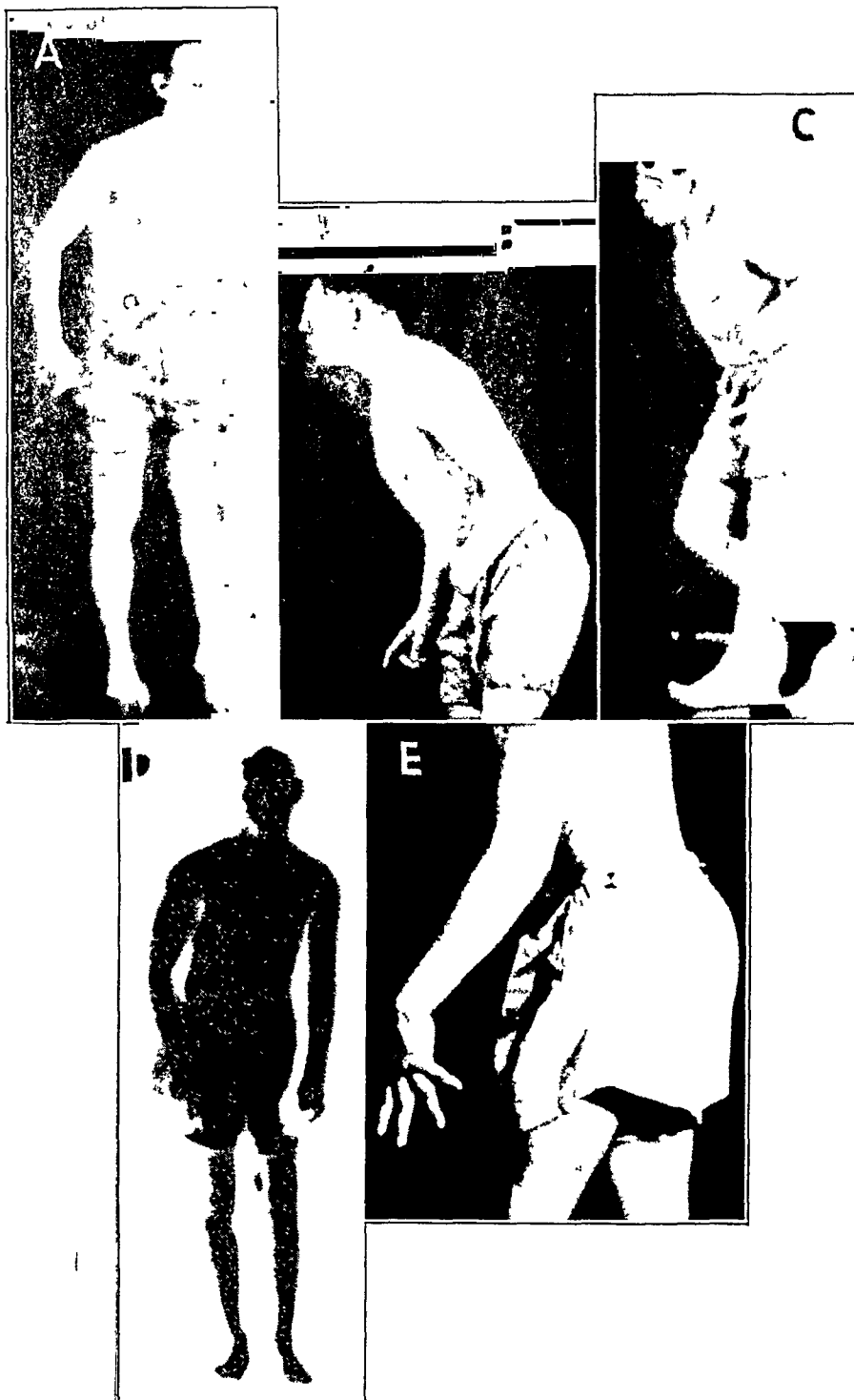
Fig. 16 (case 13).—*A*, usual posture; *B*, and *C*, increase in involuntary movements of left arm when the patient is turning around (*B*) and walking (*C*); *D* and *E*, appearance of hands eighteen days after operation. Note change of posture and increase of involuntary movements of left hand and fingers.

motor power in the left upper extremity, with decrease in the involuntary movements. The voluntary power was not of useful character or amount at the time of discharge.

Film Analysis.—The usual posture of the patient was as follows (fig. 16 *A*): The upper part of the body

and showed many reactive movements, but no involuntary hyperkinesis or tensions. At irregular intervals involuntary movements appeared in the left upper and lower extremities and in the trunk. Flexion and torsion of the trunk gradually became more pronounced, and flexion of the wrist and elbow increased until the elbow

tary movements which were almost as severe on the left side as on the right, where the spontaneous hyperkinesis was more pronounced.

After operation the position of the head is much improved. It is now held almost straight. But the position of the trunk and extremities is unchanged (fig. 15 *D* and *E*). The postural disorder and involuntary activity, both spontaneous movements and those induced by voluntary action, are not decreased. The range of voluntary movements of the head is somewhat reduced.

The history of the development of the disease in this patient is complicated. Delivery was difficult, but signs of injury of the brain at birth were not noted and development was normal in the first two years of life. At the age of 2 years the child had an acute illness, the nature of which could not be determined. The presence of a comatose condition creates the presumption that the nervous system was somewhat affected. When he was 4 years old, involuntary motor activity started in the left arm and left hand, without any recognizable cause. The motor disorder was steadily progressive during the next twenty years. An increasing number of parts were affected: the extremities, the trunk and the shoulders. At the age of 17 the neck became involved, with the appearance of extremely disturbing torticollis, and at the age of 31 further progression was reported, after an episode of unconsciousness.

Analysis of the motor symptoms revealed slow dystonic movements, which were maintained for different lengths of time and came on at irregular intervals. In addition, changes of posture were present, and abnormal positions brought on by dystonic tensions were maintained for longer periods. Alternating movements, with the characteristics of myorhythmia, occurred more often in the left arm and hand than in the right. Voluntary acts were severely interfered with by the involuntary hyperkinesis. On the right side, where the spontaneous hyperkinesis was much less pronounced than that on the left, the impairment of voluntary movements was as great as that on the left.

Neurologic examination revealed spasticity of the left extremities and greater prominence of the tendon reflexes in the left lower extremity. The Babinski sign was present bilaterally.

In this case the symptoms were not of an elective systemic character. Although dystonic symptoms were prevalent, the signs suggesting lesions of the pyramidal system cannot be neglected. The occurrence of an infectious disease, with apparent involvement of the brain, two years before the onset of the hyperkinesis must also be considered. Although there was a free interval between these two incidents (the disease of the nervous system and the onset of the involuntary movements), the disease, start-

ing at the age of 4 years, may have been caused by a lesion produced by the infection at the age of 2 years. On the other hand, the steady, slow progression of the disease, with dystonic symptoms, was similar to the course in cases in which no etiologic factor is recognizable.

It is probably wiser not to attempt classification of such complicated cases. They should be taken out of the dystonia group and considered separately until pathologic examination furnishes the explanation.

The part of the surgical procedure aimed at relief of the torticollis was successful. After the operation the head could be held straight, and no twisting occurred. The result of the anterolateral chordotomy was not convincing, but the patient reported that he had considerably more freedom in the use of his hand and trunk.

CASE 13.—*History.*—C. W., a man aged 23, was admitted to the hospital with a history of spasticity and involuntary movements since birth. Pregnancy, labor and delivery were apparently normal in every respect. The patient was a first-born child; his weight at birth was 5 pounds 6 ounces (2,388 Gm.). No abnormality was noticed until the age of 6 months, when he seemed to be unable to sit up. He continued to be clumsy and to balance poorly and did not walk until he was 4 years old.

Because of the stiffness and the uncontrolled movements of the left extremities, he was severely incapacitated, although he was able to go through public school and to complete two years of high school. At the age of 8 years he had an operation for correction of the deformity of the left foot, and at the age of 18, a second operation and transplantation of the tendon. Subsequent to the last operation the involuntary movements of the left arm were accentuated. In March 1941 administration of scopolamine was started, as a result of which he was free from symptoms for several weeks; subsequently, however, the medication has had a gradually decreasing effect.

The family history was noncontributory.

Examination.—The patient was unable to walk without assistance. The left arm showed pronounced spasticity and a tendency to pull around behind the back. There were rigid spasticity of the muscles of the forearm and flexion of the fingers. The left leg was in general smaller, and perhaps shorter, than the right leg. Muscular strength was good on the right side but could not be tested for in the left arm. The left leg appeared to be generally weak. Tests for coordination and equilibration could not be performed. The deep reflexes were present and normal on the right side but were not satisfactorily obtained on the left because of spasticity.

The sensory status was normal. The pupils were equal and reacted somewhat poorly to light. The palpebral fissure was slightly greater on the left side than on the right, and there were many involuntary movements of the muscles of the left side of the face. The rest of the cranial nerves were normal.

Laboratory studies revealed nothing abnormal.

Psychometric examination revealed a high average general intelligence.

Operation.—In November 1941 temporoparietal craniotomy was done on the right side, and procaine hydrochloride was injected into various portions of the right

His father was said to have been mentally defective; a paternal aunt was an imbecile and a dwarf, and a paternal uncle had a high temper. The patient's brother was "nervous."

After the patient's delivery he did not breathe spontaneously for about an hour. In the first few months of life he appeared to sleep during the daytime and cried all night. He began to walk at the age of 3 or 4 years. At the age of 7 or 8 the patient was called "Limpy," a nickname indicating that he walked with a limp. However, he was able to play games and maintain the pace set by the other boys. At the age of 14 he noticed his defect more, and his writing became poor because he pressed too hard on the paper. In the six years preceding admission to the hospital the difficulty

The reflexes were difficult to elicit in the left arm and could not be obtained in either leg. No pathologic reflexes were present. The abdominal reflexes were more active on the right side than on the left. At times the right pupil appeared smaller than the left, and the reaction to convergence was slight on both sides. When the patient was speaking, the left side of the face showed less innervation than the right.

The patient had a fairly well ordered mind but was emotionally unstable.

Laboratory investigations revealed nothing abnormal. Roentgenograms of the skull and the electroencephalogram showed nothing significant.

The patient was advised to submit to an operative procedure but decided against it.
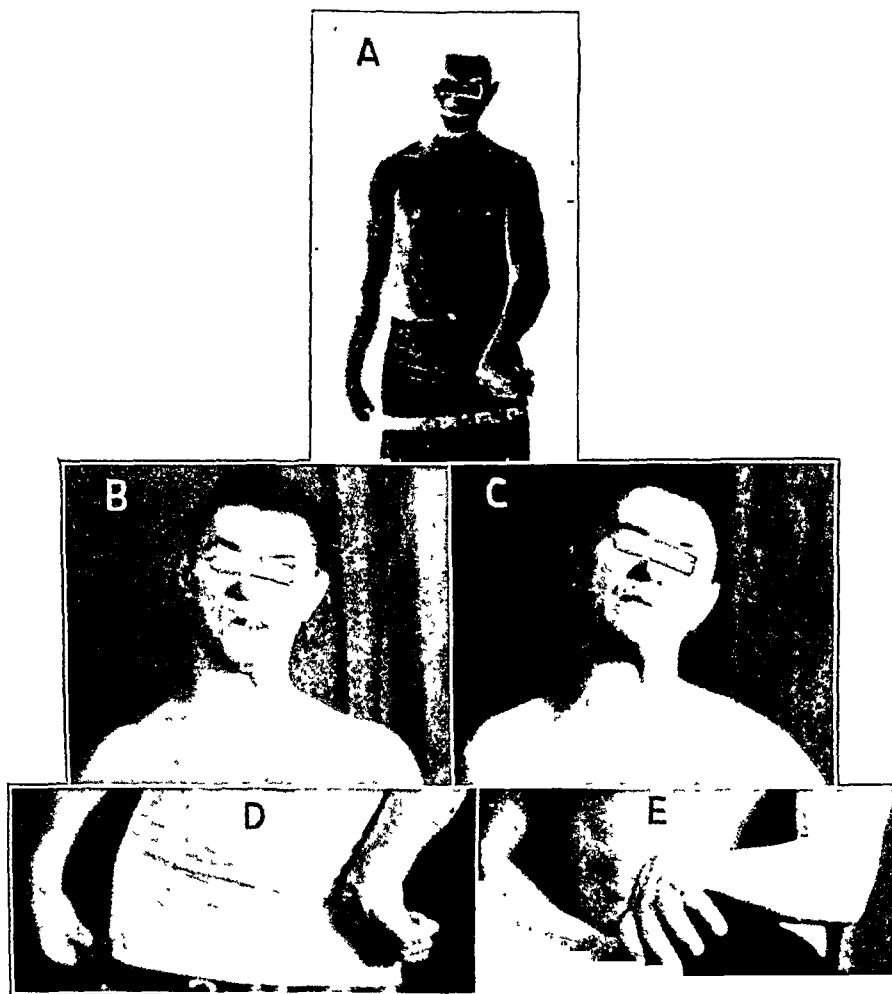
Fig. 17 (case 14).—*A*, spontaneous posture; *B* and *C*, involuntary movements of left side of face and sustained contraction of platysma muscle; *D* and *E*, voluntary opening of usually closed hand.

became more severe. When he was 19, his left hand began to draw up in a rotated position, and he found it difficult to relax his muscles. He was always able to relax after he had had a number of drinks. From the age of 14 to that of 17 he was chronically drunk.

Examination.—The patient was well nourished and well developed but pale. Enlargement of the lymph nodes was noted in the left supraclavicular and the right anterior cervical group. The blood pressure was 148 systolic and 90 diastolic.

Neurologic examination revealed that the patient was left handed. The position of the extremities and the involuntary movements will be described in analysis of the film. In walking he exhibited a steppage gait, especially noticeable in the right foot, with scraping of the toes. His voice showed jerky alterations in volume.

Film Analysis.—The patient stood (fig. 17 *A*) with the whole body slightly inclined to the left. The right arm hung in a natural position. The left arm was adducted at the shoulder joint. The forearm was slightly flexed and pronated. The hand was extremely flexed at the wrist (fig. 17 *D*). The fingers were also flexed, but the degree of flexion changed at irregular intervals and differed with each finger.

A close-up picture of the upper part of the body showed (*a*) slow, irregular movements of the muscles of the face, more noticeable on the left side than on the right, and (*b*) slow contractions of the superficial and deep muscles of the neck at irregular intervals, with some long-sustained contractions of the left platysma muscle (fig. 17 *B* and *C*). When the patient counted,

was at an angle of about 15 degrees to the upper part of the arm. The upper part of the arm was rotated backward, and as the flexion of the elbow relaxed, the arm was brought and kept as far back as possible. At the same time that the left leg was fully extended, the left foot was held in extreme plantar flexion, combined with inversion.

Every phase of the movements was sustained for a long time. The sudden change from the sustained posture is seen in figure 3 of the first article. The plantar flexion and inversion of the left foot were maintained for at least a few minutes. Suddenly, between *3* and *4*, the position changed, i. e., in one-sixteenth second.

Slow motion pictures revealed that there was no regular synergism between the various movements, that is, flexion of the elbow, adduction of the arm and twisting of the upper part of the body, which were always long sustained. There were fairly long intervals, without any movements in which the usual posture just described was maintained. During the entire series no movements of the closed fingers of the right hand were observed. The gait was impaired because the left leg was smaller and shorter than the right. Furthermore, balance was disturbed by extensive torsion and flexion of the trunk. Soon after the patient started to walk, involuntary movements set in and were sustained for a long time. Balancing movements of the right arm were abundant, but not sufficient. He fell unless he was supported. The involuntary movements of the left arm were increased when he turned around (fig. 16 *B*) and when he was walking (fig. 16 *C*).

The pictures taken eighteen days after operation showed a habitual posture quite different from that before operation (fig. 16 *D*). The trunk was only slightly bent to the left and was not twisted. The left hand was open, and the fingers were extended. At irregular intervals irregular, slow, sustained finger movements occurred (fig. 16 *E*), consisting of hyperextension and flexion of the fingers and thumb in completely irregular pattern and sequence, sometimes combined with a passing flexion of the hand. In a fairly long series, no involuntary movements of the entire left arm could be seen, and only slight twisting and bending of the trunk appeared. As the patient began to turn around, involuntary movements of the whole arm, with flexion at the elbow and adduction at the shoulder, occurred, but these movements were not so pronounced as before operation. During this voluntary action (turning around) the left hand was kept open, and there were extensive involuntary movements of the fingers.

There was pronounced paresis at the shoulder and elbow. Movements of the hand and fingers were carried out fairly well. During voluntary movements with the left arm and hand some twisting and bending of the trunk occurred.

The gait was much improved. There was no sustained tension of the left leg. Twisting and bending of the trunk were present, but were not so severe as before.

Birth was apparently normal, and no abnormalities were noticed in the first months of life. At the normal period for the appearance of coordinated motor activity, first clumsiness and then stiffness and involuntary movements of the left side of the body became apparent and persisted. General development of motor abilities was slow, and the growth of the left leg lagged behind that of the right.

Neurologic examination at the age of 23 revealed disturbances only on the left side. Pronounced stiffness of the upper and lower extremities on the left side was due to spasticity, aggravated by tensions which varied in intensity and were not constantly present. This stiffening factor produced peculiar postures of the extremities and the trunk when the muscles of the back participated. These postures showed variations in pattern and intensity. Sometimes a posture seemed to be due to a permanent contracture, resembling that associated with hemiplegia. But analysis of the film demonstrated fine differences in the positions of parts of the body. The plantar flexion and inversion of the left foot seemed to be permanent, but during the observation of a long series of pictures it suddenly disappeared from one frame to the next. The speed of this change of position can be explained only by the sudden disappearance of the additional stiffening factor.

The result of the cortical operation (extirpation of the right precentral gyrus) was remarkable. The stiffness and the tendency to transient tensions were considerably reduced. But whereas before operation the left hand was tightly closed and could be opened only after relaxation, involuntary, athetotic movements of the fingers were present after operation. They appeared predominantly as associated movements when the patient carried out voluntary acts.

The spastic hemiparesis, with underdevelopment of the left lower extremity, was presumably due to a discrete lesion of the brain stem which affected the pyramidal tract and structures lesions of which produce dystonic tensions. In spite of the report that abnormalities were not noticed during the first months of life, the disorder may have been present from birth, as motor disturbances sometimes do not come to the attention of parents before the development of motor abilities is expected. For this reason it cannot be determined whether the lesion of the brain was due to injury at birth or to an inflammatory process occurring before or shortly after delivery. In any case, the disorder started in early childhood and became more apparent only in later life, but did not really progress.

The course and the symptoms of the disease suggest the presence of a discrete lesion acquired in early childhood, and not an elective systemic disease with a tendency to progression. This case should not be included with the cases of dystonia.

CASE 14. — *History.* — E. S., a white man aged 25, entered the hospital for consideration of operative treatment.

the trunk (fig. 18 *B* and *C*), there occurred twisting movements of the pelvic portion (alternately to the left and to the right) (fig. 18 *D*), flexion and extension, mixed with rotation, of the leg, and, finally, complex movements of the trunk and the left thigh and leg which resembled kicking (fig. 18 *E* and *F*). The right lower extremity was constantly flexed at the knee and was only passively moved by the movements of the trunk.

Such an attack of involuntary movements took only a few seconds. Afterward the patient lay completely

The outstanding feature of the intricate hyperkinesis in this case was the occurrence in attacks of a storm of involuntary movements. Between these attacks the patient lay relatively quiet. Only antagonist tremor of the right hand was present, and slight changes in the position of the trunk and extremities were noticeable. At irregular intervals a wave of wormlike movements moved swiftly down the trunk, associated with throwing, flail-like movements of the left
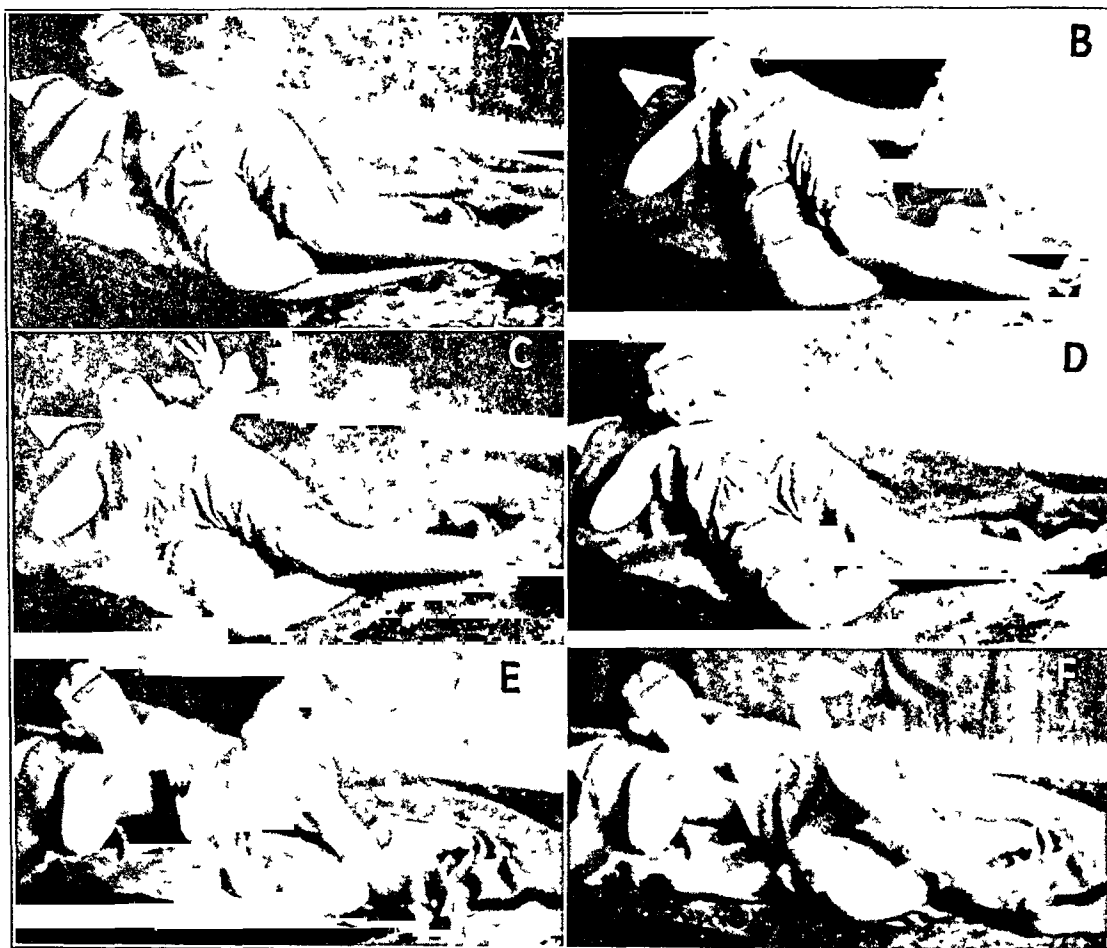
Fig. 18 (case 15) —More complicated throwing and kicking movements, in addition to dystonic movements and postures.

quiet, only an alternating tremor of the right hand and fingers persisting. This tremor was present during some attacks also.

After operation the posture was the same as before. The antagonist tremor of the right hand was not influenced. The involuntary movements during the attacks did not show any change. Perhaps the duration of the attacks was shorter.

After spontaneous delivery, disturbances were not noticed until the child was 8 months old, when weakness of the left arm became apparent. At the time he began to walk considerable spastic hemiparesis of the left side existed. At the age of 11 or 12 years involuntary movements of the left side began and progressed rapidly. A few years later the right side, too, showed stiffness and involuntary movements.

arm and alternating kicking movements of the lower extremities. There were some slow, athetotic movements of the left hand and fingers, and the alternating tremor of the right hand per-
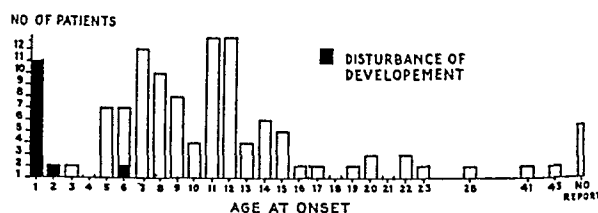
Fig. 19.—Age distribution at onset of first symptoms.

sisted during some attacks. There was a gradual increase in intensity of the hyperkinesis up to the height of the attack; then in a few seconds the storm gradually subsided. The attacks came on

the hyperkinesis of the muscles of the face and neck was much- increased.

A close-up view of the left forearm and hand as they were supported by the examiner showed that the patient was able to open his hand and to reduce the flexion of the wrist voluntarily (fig. 17 *E*). Alternate opening and closing of the hand was sometimes interrupted by extreme flexion of the wrist and of the fingers, with adduction of the thumb. After a while the tension relaxed, and the alternating movements were resumed.

If the patient pressed the hand of the examiner with his right hand, extreme tensions of the left hand and the fingers appeared, as synergistic movements. The patient could not overcome the flexion of the hand and fingers, and voluntary movements of the left hand were impossible while he was pressing with the right hand.

In walking he showed some circumduction of the left leg, with dropping of the foot. Associated movements of the left arm, which was held in the aforedescribed position, were remarkably less than those of the right arm.

The patient came of a family with several defective members. After his delivery he showed severe general disturbances, which suggested an injury of the brain at birth. Left hemiparesis had been present since early childhood, and the development of motor functions was retarded. Involuntary movements and tensions appeared much later. At the age of 14 years voluntary action. particularly that of writing, was interfered with, but not before the age of 19 did dystonic movements and sustained tensions become conspicuous.

Neurologic examination at the age of 25 revealed left spastic hemiparesis with slow, involuntary movements of the corresponding side of the face, long-sustained dystonic movements of the platysma muscle and the superficial and deep muscles of the neck and extreme tensions of the upper and lower -extremities, all on the left side. The almost constant flexion of the left hand and fingers was not due to a spastic condition. When relaxation occurred spontaneously or was brought about voluntarily, voluntary movements could be carried out, although they were suddenly arrested by involuntary tensions and abolished for some time. These dystonic tensions appeared sometimes as associated movements. When, for instance, strong voluntary movements were carried out with the right hand, tensions appeared in the left hand. The left hand could not be relaxed voluntarily before the voluntary movement of the right hand ceased.

In this case the dystonic phenomena were associated with spastic hemiparesis. There is no question of the presence of an elective systemic disease. A discrete lesion of the brain, probably caused by birth injury, was responsible for the disturbance. Notable was the particularly long interval between the injury and the onset of the hemiparesis. on the one hand, and the outbreak of the dystonic symptoms, on the other. The hemiparesis was present from early childhood, whereas the abnormal involuntary motor activity was not noticed before the age of 14 and became pronounced at the age of 19 years.

CASE 15.—*History.*—R. J., a white man aged 21, was born without apparent trauma, delivery being spontaneous. There were no subsequent convulsions. When he was about 8 months old weakness of his left hand and drooping of his head to the left were first noted. When he started to walk, at 3 years of age, gross weakness of the left leg was apparent; this leg also seemed somewhat stiff, and he walked and ran in a limping fashion. At about 11 years of age, without a history of preceding trauma of the head or infection, the patient began to have involuntary movements of his left arm, which gradually became more severe. At 12 years of age he began to have involuntary movements in the left leg also. At 14 years of age he became bedridden. During the two years preceding admission to the hospital he had an occasional sensation of tightness of the right lower extremity, associated with clonic movements of the right hand and arm.

The family history did not reveal a hereditary tendency.

Examination.—General examination revealed nothing abnormal except for the motor incapacity and the involuntary movements. He could not stand erect, even when aided. The head drooped forward as he slumped in an attempt to sit erect. The muscles of the right arm and leg showed increased resistance to passive movements. There was weakness of the left arm and leg, most noticeable in the dorsiflexor muscles of the wrist and fingers. Speech was fairly good, although a bit scanning and high pitched when he was excited. The deep reflexes were slightly more active in the upper and lower extremities on the right side than on the left. The abdominal reflexes were absent on the left side. The Hoffmann sign was elicited on the right, but there was no Babinski sign. The cranial nerves were normal except for myopia of 6 D. and a few ill sustained nystagmoid jerks on lateral gaze.

The results of laboratory examinations were noncontributory.

The mental status was normal.

Operation.—A cervical laminectomy was performed. The left anterior funiculus of the cord was cauterized between the second and the third cervical segment.

Film Analysis.—The patient was lying on the floor (fig. 18 *A*). The head was hyperextended and turned to the right. The left arm was adducted and flexed at the elbow and the wrist. The right arm was abducted at the shoulder, extremely flexed at the elbow and slightly flexed at the wrist. The left leg was rotated inward. The right leg was slightly flexed at the knee, and the right foot was extremely supinated and dorsiflexed, with extension of the toes.

This position was maintained for a time. Suddenly a severe attack of hyperkinesis started. The head and the right arm remained in the same position. The left arm made throwing movements as a whole, while the forearm, flexed at the elbow, swung around in wide, irregular, circling movements. The left hand was held with the fingers extended but was flexed at the metacarpophalangeal joints, and the thumb was adducted.

Waves of involuntary movements started at the same time in the trunk, later affecting the pelvis and the left lower extremity. After strong hyperextension of

Table 1.—Cases with Dystonic Symptoms Reported in the Literature *

Case No.	Year of Report	Author	Sex	Delivery	Develop-ment	Age of Onset, Yr.	Familial Occurrence	Group	Diagnosis
1	1893	Gowers	M	..	..	9	One brother with same disease	A	"Tetanoid chorea"
2	1901	Desterac	F	+	+	?	....	A (probably D)	Spasmodic torticollis
3	1908	Schwalbe	1 F	..	+	11 }		D	Tonic spasm with hysterical
4			2 M	..	..	12 } Same family		D	symptoms
5			3 ?	..	+	14]		D	
6	1911	Ziehen	F	..	+	7	....	D	Tonic torsion neurosis
7	1911	Oppenheim	1 F	+	+	9	....	D	Dystonia musculorum defor-
8			2 F	+	+	12	....	D	mans; dysbasia lordotica
9			3 M	+	+	14	....	D	progressiva
10			4 ?	+	+	12	....	D	
11	1911	Flatau and Sterling	1 M	..	..	7	....	D	Progressive torsion spasm in
12			2 M	+	+	11	....	D	children
13	1911	Higier	F	..	+	19	....	A	Tonic-clonic movements
14	1912	Fränkel	1 M	+ (Forceps)	+	11	....	D	Tortipelvis
15			2 M	+	+	19	....	D	
16			3 M	+	+	10	....	D	
17			4 M	+	Injury, convul- sions —	..		A	
18	1912	Bregman	1 M	..	..	16	....	D	Spasmodic condition, juvenile
19			2 M	..	..	18	....	A	form
20			3 M	..	..	14	....	D	
21	1912	Bernstein	M	..	..	12	One brother with same disease	D	Torsion cramp
22	1913	Abrahamson	F	+	+	8	....	D	Dystonia musculorum defor-mans
23	1913	Bonhoeffer	M	..	..	?	....	D	Torsion spasm
24	1913	Bregman	F	..	..	8	....	D	
25	1913	Spiller	M	..	—	Middle age	Two feebleminded sisters with chorea	A	Dystonia musculorum defor-mans
26	1914	Beling	F	+	+	7	....	D	Dystonia musculorum defor-mans
27	1914	Haenisch	M	..	..	?	....	A	Progressive torsion spasm
28	1914	Kroll	M	..	—	Post-partum onset	....	D	Double athetosis
29	1914	Seelert	M	+	+	6	....	D	Progressive torsion spasm
30	1915	Biach	M	..	..	15	....	D	Dystonia musculorum defor-mans
31	1915	Climenko	F	+	+	9	....	D	Dystonia musculorum defor-mans
32	1916	Sterling	M	..	..	14	....	D	
33	1916	Diller and Wright	M	..	..	Before age of 14	....	D	Dystonia musculorum defor-mans
34	1916	Patrick	1 M	..	..	Middle age	....	A	Dystonia musculorum defor-mans
35			2 M	..	..	?	....	A	
36			3 M	..	..	?	....	A	
37	1916	Hunt	1 M	..	..	8	....	D	Progressive torsion spasm of
38			2 M	+	+	6	....	D	childhood
39			3 M	..	..	9	....	D	
40			4 F	..	..	10	....	D	
41			5 F	..	..	11	....	D	
42			6 F	..	..	17	....	D	
43	1917	Weisenburg	M	+	+	6	....	D	Unusual torsion spasm
44	1917	Dercum	M	+	+	19	....	A	Anomalous torsion spasm
45	1917	Hallock and Frink	F	+	+	5	....	D	Dystonia musculorum defor-mans
46	1918	Keschner	F	+	+	12	....	D	Dystonia musculorum defor-mans
47	1918	Kramer	M	..	..	47	....	B	Torsion spasm in adult
48	1918	Thomalla	M	+	+	13	....	B	Torsion spasm
49	1919	Mendel	1 M	+	+	13	....	D	Torsion dystonia
50			2 F	+	+	5	....	D	
51	1920	Frauenthal and Rosenheck	F	+	+	7	....	D	Dystonia musculorum defor-mans
52	1920	Abrahamson	1 F	+	+	12	Same family (brother and 2 sisters)	D	Familial dystonia of Oppen-heim
53			2 F	..	..	?		D	
54			3 M	..	..	?		D	
55	1920	Taylor	1 M	+	+	7	Same family (brother and sister)	D	Dystonia lenticularis
56			2 F	+	+	7		A	Dystonia musculorum defor-mans
57	1920	Collier (Blandy)	M	+	+	5	Sister with infec-tious chorea	D	Torsion dystonia
58	1920	Spiller	F	..	+	5	....	D	Acquired double athetosis; dystonia lenticularis
59	1921	Dawidenkow and Zolotowa	M	..	..	13	One sister and one daughter with same disease	A	Dystonia musculorum defor-mans
60	1921	Price	1 M			3	Twins	A	Dystonia lenticularis in twins
61			2 M			..	....	A	

* In this table, the plus sign indicates normal delivery or development; the minus sign, abnormal delivery or development, and .. no data.

without any recognizable reason at rather irregular intervals. There was no loss or change of consciousness during the attack.

Neurologic examination revealed evidences of damage of the pyramidal tract on both sides, nystagmoid jerks on lateral gaze and considerable paresis of the left arm and leg.

The symptoms differed considerably from those in the preceding cases. Hyperkinetic attacks alternated with states of relative rest. During the latter, there were present only alternating tremor of the right hand and positions resembling dystonic postures, together with hemiparesis and signs of defect in the pyramidal tract on both sides. During the attack a more complicated pattern of involuntary movements was predominant. Twisting and turning movements of the head, trunk and arms were mixed with mass movements resembling complicated acts, such as rolling around or kicking. The mechanism of some of these movements was similar to that of athetotic and dystonic movements, but others showed a pattern resembling that of purposive movements.

From the clinical data alone one cannot classify this disease, which was presumably present at birth, with one of the known disease entities. At any rate, it should not be included with the dystonias.

The anterolateral chordotomy was without notable effect.

SUMMARY OF CLINICAL OBSERVATIONS

Common to all the cases was the occurrence of dystonic symptoms of the kind described as dystonic movements and postures in the first paper in this series.[1] The predominance of these motor symptoms in almost all cases induced the observers to suggest the diagnosis of dystonia. But after consideration of all available clinical data one may proceed to define better circumscribed clinical groups.

In the first 4 cases the significant clinical data are similar. After a normal delivery and an uneventful development during the first years of life, dystonic symptoms gradually appeared, between the ages of 8 and 13 years, and steadily progressed in severity. No apparent cause for the cerebral disorder could be found. The abnormal involuntary motor activity was the only disorder of the disease. One may, therefore, speak of a selective systemic symptomatology.

Cases 7 and 8 differed only slightly from the first cases. Dystonic symptoms constituted, again, the only feature of a disease which developed gradually in completely healthy persons. Significant are the onset of the first symptoms at a later age (18 and 23 years) and the particularly slow progress of the disease to involve circumscribed portions of the body. In case 8, in which the onset was at the age of 23, dystonic symptoms were present only in the muscles of the neck, shoulder and trunk; in case 7 in which onset was at the age of 18, dystonic tensions in the muscles of the thigh and back progressed so slightly that they usually were noticed only by the patient herself. In case 6 an earlier onset, with a feeling of tightness in one arm, was reported. Not before the age of 15 were motor disorders noticed, and then they progressed slowly. Many years later they were confined to the neck, trunk and arms.

In cases 9, 10 and 11 also dystonic symptoms were the only symptom of the disease, but they had been present since early life. Although some disturbances were observed after delivery (underdevelopment and cyanosis in case 9; convulsions in cases 10 and 11), birth injury does not seem to have been the cause of the cerebral lesion. The degree of progression in these cases was remarkably severe; in cases 9 and 11 the patients' conditions were the most pitiful in this series.

The disorder in case 5 consisted also exclusively of dystonic symptoms. They gradually developed from the age of 10 years and progressed relatively slowly. But, unlike the state in cases 1 and 4, early physical and mental development was rather slow, and the latter apparently was incomplete. One must, therefore, assume that the nervous system was somewhat subnormal at birth and, in addition, that a progressive process existed at the age of 10 years.

With respect to symptoms, development and etiologic considerations, cases 1 to 11 were similar. Without a recognizable etiologic agent, selective systemic motor disorders developed. Only dystonic symptoms were present, without other neurologic signs. These movements gradually developed, progressing and spreading over the whole body, or only over some areas.

Although I am aware that these statements are corroborated by clinical evidence alone, I suggest that the symptoms described be taken as characteristic of the dystonia group. This group consists of 4 cases of the juvenile form, with the onset of the disease between the ages of 8 and 13 years, and 3 cases of the late form, with the onset after the age of 15 years. In these 7 cases no disturbance of early development was observed. In 3 cases of early onset the motor disorder started shortly after delivery, and one must assume that the basic cerebral process was already present at birth. With respect to the onset of the disease 1 case belonged to the juvenile form, but early disturbance of development suggests the existence of an abnormality of the brain at birth.

Case No.	Year of Report	Author	Sex	Delivery	Development	Age of Onset, Yr.	Familial Occurrence	Group	Diagnosis
123-137	1929	Brzezicki....................				..	....	A	Torsion dystonia
138	1930	Lafora.......................	M			..	....	A	
139	1930	Stern........................	?	..	..	12	....	D	Dystonia
140	1930	Brunschweiler..............				..	....	A	Abortive torsion spasm
141	1930	Regensburg.................	1 M	..	+	11	Several cases in family	D	Dystonic torsion symptom complex
142			2 M	..	..	11	Nephew of first patient	D	
143	1930	von Hallervorden...........	?	..	..	22	....	B	Athetosis with symptoms of torsion spasm
144-148	1930	Fracassi and Marelli........				..	....	A	Torsion spasm
149	1930	Cudnow......................	?	..	..	13	....	A	Torsion spasm
150	1931	Seidemann..................	F	..	+	2	....	A	Torsion spasm
151	1931	Luethy (case 3 of Jakob [1932])	?	..	..	18	....	B	Hepatolenticular degeneration
152	1931	Dias (case 2 of Jakob [1932])	F	..	.. Debility	10	....	B	Torsion dystonia
153	1931	Ramos Fernández...........	1 M	..	..	15	....	D	Torsion spasm
154			2 ?	—	—	Post partum	....	A	
155	1931	Vizioli......................	?	+ Premature	..	?	....	B	Torsion spasm
156	1932	Jakob.......................	1 M 2 [Dias] 3 [Luethy]	..	..	15	....	D	Torsion spasm
157	1932	Garland....................	M	..	+	5	....	A	Torsion spasm; dystonia lenticularis
158	1932	Budde.......................	?	..	..	6	....	D	Torsion dystonia
159	1932	Schmitt and Scholz..........	M	..	+	22	....	D	Torsion dystonia
160	1932	Dubitscher.................	?	+	+	6	....	B	Hyperkinetic-dystonic syndrome
161	1932	Laruelle and Divry..........	F	..	+	31	....	A	Torsion spasm
162	1932	Rakonitz....................	F	..	..	23	....	A	Exogenous unilateral torsion dystonia
163	1932	Saegesser..................	F	..	..	28	....	D	Torticollis spastica
164	1933	Foerster....................	M	..	..	20	....	D	Torticollis
165	1933	Noble de Mello and Quintanilha	M	..	..	33	....	B	Dystonia
166	1934	Quadfasel and Krayenbühl..	M	..	..	15	....	D	Torticollis spastica
167	1934	Santangelo.................	1 F	..	..	9	Three sisters with disease	D	Dysbasia lordotica, familial type
168			2 F	..	..	9		D	
169			3 F	..	..	9	....	D	
170	1934	Agostini....................	F	..	..	10	....	B	Torsion spasm
171	1936	Zádor.......................	M	+	+	10	....	D	Torsion spasm
172	1935	Beilin......................	M	+	+	11	....	D	Torsion syndrome
173	1935	Munch-Petersen..............	M	..	+	18	....	A	Torsion dystonia
174	1937	Paulian and Cardas.........	1 F	..	..	33	....	B	Torsion spasm
175			2 M	..	..	35	....	A	
176			3 M	..	..	8	....	A	
177			4 M	..	..	5	....	A	
178			5 M	..	..	5	....	D	
179	1938	Davison and Goodhart......	1 F	..	—	6 wk. post partum	....	D	Dystonia musculorum deformans
180			2 F	..	+	14	....	D	
181			3 M	..	+	8	....	D	
182			4 M	..	+	7	....	D	
183	1938	Maspes and Romero.........	M	..	..	..	....	A	Torsion spasm with athetosis
184	1939	Gordin.....................	M	..	+	22	....	A	Unilateral torsion dystonia
185	1940	Benedek and Rakonitz.......	1 F	..	—	Post-partum onset	....	D	Myoclonic torsion dystonia
186			2 F	..	..	Childhood	Mother of first patient and	A	
187			3 M	..	+	..	brother of first patient	A	
188	1941	Nielsen.....................	M	+	—	18 mo.	....	D	Dystonia musculorum deformans

The clinical data common to the first 11 cases are in such definite contrast to the data for the last 4 cases that the latter should be classified separately. In case 14 hemiparesis was combined with unilateral dystonic symptoms. The disorder was presumably due to injuries of the brain at birth, as suggested by the disturbances after delivery. In case 13 the same symptoms were presented—spastic hemiparesis with unilateral dystonic tensions. The disease came on in early childhood and did not progress. The condition was presumably due to a lesion in the brain stem of infectious or vascular origin.

In case 12, whenever dystonic symptoms appeared, there were, in addition, signs of a lesion of the pyramidal system. At the age of 2 years the patient had an acute disease of the central nervous system, and the motor disorders, starting at the same time, may have been due to the former disease. These facts being taken into consideration, classification of such cases should be postponed.

Case No.	Year of Report	Author	Sex	Delivery	Development	Age of Onset, Yr.	Familial Occurrence	Group	Diagnosis
62	1922	Patrick	M	+	—	6	Other twin died of cerebellar glioma	D	Dystonia musculorum deformans
63	1922	Yawger	?	—	—	Post-partum onset		D	Dystonia musculorum deformans
64	1921	Wimmer	F	—	—	10		B	Progressive torsion spasm, infantile form
65	1921	Flater	F	..	—	8		D	Torsion dystonia
66	1922	Wartenberg	M	..	..	Puberty		D	Torsion dystonia
67	1922	Fossey	F	..	..	23	Six relatives with chorea; 1 brother with dystonia	B	Dsytonia musculorum deformans
68	1922	Wechsler and Brock	1 M	..	..	11		D	Dystonia musculorum deformans
69			2 M	..	..	8		D	
70			3 F	..	..	12	Four others with disease in family	D	
71			4 M	..	..	11		D	
72			5 M	..	..	?		D	
73			6 F	..	..	8		D	
74	1922	Jacob	M	..	—	12		D	
75	1922	Rosenthal	1 F	..	—	12		D	Torsion dystonia
76			2 M	—		6		D	
				8 mo. child					
77	1922	Cassirer	1 M	..	..	41		D	Torticollis and torsion spasm; dystonia musculorum deformans
78			2 M	..	—	7		D	
79	1922	Ewald	M	—	—	9		D	Torsion dystonia
80	1922	Pollock	F	..	..	43		D	Dystonia
81	1923	Rosenthal	1 M	—	—	10		A	Cerebral disease at early age
82			2 F	—	—	7		D	
83	1923	Margaretten	F	—	—	2 wk. post partum		D	Dystonia with athetoid features
84	1923	Solomon	1 ?	..	..	?		A	Dystonia lenticularis
85			2 ?	..	..	?		A	
86	1923	Wartenberg	M	+	+	11		D	Torsion dystonia
87	1923	Richter	F	+	+	11		D	Torsion dystonia
88	1924	Fraenkel	1 F	..	..	40		B	Dystonic syndrome
89			2 F	..	..	12		D	Torsion dystonia
90	1924	Prissmann	M	+	+	8		D	Torsion dystonia
91	1925	Itzenko						A	
92	1925	Stertz	M	..	+	7		D	Torsion spasm
93	1925	Urechia, Mihalescu and Elekes	M	+	+	6		B	Dystonia lenticularis
94	1925	Moser	1 F	..	+	11		D	Organic torticollis
95			2 F	..	+	23		D	
96	1926	Roussy and Levy	F	..	..	60		B	Torsion spasm
97	1926-1927	Marotta	1 M	+	+	7		D	Torsion dystonia
98			2 M	+	+	11		B	
99			3 M	+	—	Post-partum onset		D	
100			4 M	+	..	7		B	
101	1927	Heuyer and Badonnel	F	..	..	9		A	Torsion spasm
102	1927	Chavany and Morlaas	F	..	..	17		B	Torsion spasm
103	1927	Navarro and Marotta	M			..		A	
104	1927	Chiari	M			..		B	Hemilateral torsion spasm
105	1928	Austregesilo and Marques	1 F	—	—	7 mo.		D	Dystonia
106			2 M	..	+	13		A	
107			3 M	—	—	..		A	
108	1928	Kleist and Herz	1 M	—	—	Post-partum onset		A	Congenital defect
109			2 M	+	+	22		D	Torsion dystonia
110	1928	Marotta	F	..	..	4		A	Torsion dystonia
111	1929	Zolotova	1	—	—	Post-partum onset		D	Torsion syndrome in children
112			2	—	—	..		D	
113	1929	Marinesco and Nicolesco	F	..	+	15		D	Spasmodic contorsional dystonia
114	1929	Roasenda	1 F	..	..	40		B	Torsion spasm
115			2 F	..	..	40		B	
116			3 M	..	..	28		B	
117	1929	Laruelle and van Bogaert	?	..	—	Post-partum onset		D	Syndrome of rigidity with torsion spasm
118	1929	Bouman	M	+ (forceps)	+	5		D	Torsion spasm
119	1929	Laruelle	M	—	+	12		D	Torsion spasm
120	1929	Léri, Layani and Weill	F	+	+	3		D	Dystonia
121	1929	Mankowsky and Czerny	1 M	..	..	7	Congenital cardiac defect in family; 1 sister with same disease as patient	D	Torsion dystonia
122			2 F	..	..	8	Brother of preceding patient	D	

which the motor disturbances started shortly after birth.

The symptoms in the reported cases were studied carefully in order to find differences in the three groups. In most cases of early onset involuntary movements seemed to prevail over dystonic postures and long-sustained lesions. But in other cases of early onset, e. g., in case 9 of the present series, particularly significant dystonic tensions and postures were presented. As a matter of fact, from the symptoms alone, without knowledge of the history of the development of the disease, it is not possible to state the time of the onset of the disease in the majority of cases.

Frequently, in cases of late onset only torticollis was presented at the onset of the disease. Dystonic movements and tensions of the neck and shoulders appeared first; later, the trunk and extremities became involved. Only cases in which there was progression of involuntary movements and tensions from the head to other parts of the body are considered in this paper. The problems connected with pure torticollis will be analyzed separately. It may only be mentioned that the disorder in the cases of pure torticollis begins predominantly, or perhaps exclusively, at a later age, so that the number of cases of late-appearing dystonia could be considerably increased by inclusion of the cases of torticollis.

The predominant occurrence of dystonia in families of Russian Jewish descent was striking in the first observations on this disease. Later, cases which did not belong in this racial group were described, and in the last ten years instances of dystonia have been found in the population of almost all countries of the world, without respect to race. I have not elaborated on the possible prevalence of dystonia in any one group. Similar observations on other diseases of unknown origin (e. g., infantile amaurotic familial idiocy, or Tay-Sachs disease) had to be taken as fact. On the other hand, recent experiences with *Rassebiologie* have been so depressing and grotesque that they do not encourage speculations.

Familial occurrence has been reported only in 8 instances. In the cases of Schwalbe (1908), Bernstein (1912), Abrahamson (1920), Wechsler and Brock (1922), Mankowsky and Czerny (1929), Regensburg (1930), Santangelo (1934) and Beilin (1935), several members of the same family had dystonia. Patrick (1921) described a twin with this disease; his twin brother died of a cerebellar glioma. The character of the disease of the twins reported on by Price is not clear. The occurrence of convulsions and optic nerve atrophy does not make the diagnosis of dystonia probable. Kehrer, in his analysis of the *Erblichkeitskreis* of torsion dystonia, did not consider in sufficient detail the difference in genesis and origin. His own case of "progressive torsion dystonia with idiocy and retinitis pigmentosa" surely does not belong with the cases of dystonia. The largest number of diseased members in the same family was reported by Regensburg, who concluded that there was "an exquisitely hereditary, or familial, character in a series of cases." But from his description the diagnosis of dystonia appears doubtful for some members of the family. My own experience leads me to agree rather with Mendel (1936) that hereditary factors are not traceable in the majority of cases of dystonia.

CONCLUSIONS

1. Dystonic movements and dystonic postures are symptoms of an organic nervous disease. Their occurrence alone does not enable one to make the diagnosis of a disease entity.

2. On the basis of all the available clinical data, the clinician is able to separate cases which are classifiable under well known diseases, such as chronic epidemic encephalitis, Wilson's disease and Huntington's chorea. Neither these cases nor other cases in which appear gross lesions of known character, such as tumor, vascular lesions and birth injuries, should be included with the dystonias.

3. The diagnosis of "dystonia" should be made only in cases with the following clinical characteristics: (*a*) selective systemic symptoms in the form of dystonic movements and postures, and (*b*) gradual development, without recognizable etiologic factors at the onset.

4. The dystonias may be further classified into the early form, with an onset at or shortly after birth; the juvenile form, with an onset between the age of 5 and 15 years, and the late form, with an onset after the age of 15.

700 West One Hundred and Sixty-Eighth Street.

BIBLIOGRAPHY

Gowers, W. R.: A Manual of Diseases of the Nervous System, Philadelphia, P. Blakiston, Son & Co., 1893.

Desterac: Torticolis spasmodique et spasmes functionelles, Rev. neurol. **1**:591, 1901.

Schwalbe, W.: Eine eigentümliche tonische Krampfform mit hysterischen Symptomen, Inaug. Dissert., Berlin G. Schade, 1908.

Flatau, E., and Sterling, W.: Progressiver Torsionspasmus bei Kindern, Ztschr. f. d. ges. Neurol. u. Psychiat. **7**:586, 1911.

Higier, H.: Ein Fall von Dystonia musculorum progressiva deformans, abstracted, Jahresb. u. d. Leistung. d. Neurol. u. Psychiat. **15**:663, 1911.

Oppenheim, H.: Ueber eine eigenartige Krampfkrankheit des kindlichen und jugendlichen Alters (Dysbasia lordotica progressiva, Dystonia musculorum deformans), Neurol. Centralbl. **30**:1090, 1911.

Ziehen: Ein Fall von tonischer Torsionsneurose, Neurol. Centralbl. **30**:109, 1911.

The disorder in case 15 started in early childhood and was progressive. Dystonic movements could be observed, but the occurrence of attacks of more complicated hyperkinesia did not fit in the pattern of the dystonia group. Cases with such uncommon symptoms should be separated as representing an "unknown progressive disease of early childhood with involuntary movements."

REVIEW OF CASES IN THE LITERATURE

To supplement and test this clinical material and the aspects of the classification outlined, all the cases reported in the literature were reviewed and the clinical data reexamined. In table 1 are presented the data on 188 cases with symptoms of dystonia published since the first detailed description by Schwalbe.

Of these 188 cases, the given or available data for 61 cases did not seem adequate for diagnostic consideration. (These cases are designated as group A.) In another 22 cases the clinical signs and symptoms, and in some instances the pathologic picture after anatomic investigation, leave no doubt that they must be classified under other, well known disease entities. (These cases are designated as group B.) This group contains 4 cases of Huntington's chorea (chronic progressive chorea); 4 cases of Wilson's disease (hepatolenticular degeneration); 11 cases of chronic epidemic encephalitis; 2 cases in which there were vascular lesions, and 1 case of Hallervorden-Spatz disease. After elimination of groups A and B, 105 of the 188 cases remain. (These cases form group D.) They must be assigned to the preliminary "dystonia group," as previously outlined. A more or less progressive disease developed without known cause. During the entire course, involuntary motor activity in the form of dystonic movements and postures characterized the disturbance; no other disorders were revealed by neurologic examination. The three groups may be summarized as follows:

		No. of Cases
Group A	Report available incomplete or diagnosis unconfirmed	61
Group B	Condition classifiable with other well known diseases	22
Group D	Dystonia	105
	Total	188

Table 2 and figure 19 show the age distribution for cases of the dystonia group at the onset of the first symptoms. In 10 cases, or 9.5 per cent, the disease appeared immediately after the delivery or in the first few weeks of life (early form). In the majority of cases, 78, or 74.3 per cent, the onset of the disease was between the ages of 5 and 15 years (juvenile form).

In a third, much smaller, group the first symptoms started at a more advanced age (late form).

All reports were carefully examined with respect to disturbances during and after delivery and retardation of development. Instrumental delivery was regarded as significant only if objective signs observed immediately post partum indicated the presence of impairment of the nervous system. As can be seen from table 3, both the

TABLE 2.—*Age Distribution at Onset of First Symptoms*

Form	No. of Cases	Percentage
Early	10	9.5
Juvenile	78	74.3
Late	11	10.0
Total number of cases in which age was reported at onset of disease	99	

delivery and the development were reported to be normal in 34 cases. In 18 additional cases the development was normal, but no exact information on the delivery was given. Thus, in 52 of 105 cases (49.5 per cent) there was certain normal development until the onset of the first symptoms of the disease. After normal delivery, retardation of development was seen in 4 cases; both disorders after delivery and retardation of development were present in 4 cases, and retardation of development without any report on delivery was noted in 4 cases. Altogether, in 12 of 105 cases (11.5 per cent) there was retardation of development. Only in 1 case were there disorders shortly after birth and later normal

TABLE 3.—*History of Delivery and Development in One Hundred and Five Cases*

Delivery normal; development normal	34	52 (49.5%)	Normal development
No exact report on delivery; development normal	18		
No exact report on delivery or development	40	39.0%	
Delivery with disorders; development normal	1		
Delivery normal; development incomplete	4	12 (11.5%)	Incomplete development
Delivery with disorders; development incomplete	4		
No report on delivery; development incomplete	4		

development. In 40 cases no report on delivery or development was given. In summary, development was normal until the onset of the first symptoms in 52 cases (49.5 per cent) and was retarded in 12 cases (11.5 per cent). In only 2 cases of the infantile form was there retardation of development, whereas it was present, of course, in all cases of the early form, in

Itzenko, V.: Fall von doppelter Athetose mit Ziehen'schem Torsionsspasmus, Zentralbl. f. d. ges. Neurol. u. Psychiat. 41:630, 1925.

Moser, K.: Ueber organisch bedingte Halsmuskelkrämpfe, Arch. f. Psychiat. 72:259, 1925.

Stertz, G.: Fall von Torsionsspasms, Zentralbl. f. d. ges. Neurol. u. Psychiat. 40:442, 1925.

Urechia, C. I.; Mihalescu, S., and Elekes, N.: Contribution anatomoclinique a l'étude de la dystonie lenticulaire (Spasme de torsion), Rev. neurol. 2:177, 1925.

Roussy, G., and Levy, G.: Phénomènes de décérébration, de torsion spasmodique et d'athétose, Ann. de méd. 20:460, 1926.

Marotta, A. S.: Los diversos periodes evolutivos de la distonia de torsion, Rev. méd. latino-am. 12:214, 357 and 538, 1926-1927.

Chavany, J. A., and Morlaas: Sur une varieté spéciale de spasme de torsion, Rev. neurol. 1:629, 1927.

Chiari, R.: Ueber einen Fall von halbseitigem Torsionsspasmus, Wien. klin. Wchnschr. 40:287, 1927.

Heuyer, G., and Badonnel, H.: Spasme de torsion, Rev. neurol. 2:645, 1927.

Navarro, J. C., and Marotta, A. S.: Dystonia musculorum deformans ou spasme de torsion, Rev. méd. latino-am. 140:1144, 1927.

Austregesilo, A., and Marques, A.: Dystonies, Rev. neurol. 2:562, 1928.

Kehrer, F.: Erblichkeit und nervenleiden, Berlin, Julius Springer, 1928.

Kleist, K., and Herz, E.: Torsionen und Torsionsdystonie, Med. u. Film. 16:124, 1928.

Marotta, A. S.: Beitrag zum Studium der Torsionsdystonie, Zentralbl. f. d. ges. Neurol. u. Psychiat. 48:416, 1928.

Bouman, L.: Un cas de spasme de torsion, Rev. neurol. 1:46, 1929.

Brzezicki, E.: Ueber Dystonie oder Torsionskrampf, Polska gaz. lek. 8:885, 1929; abstracted, Zentralbl. f. d. ges. Neurol. u. Psychiat. 56:670, 1930.

Laruelle, L.: Un cas de spasme de torsion unilatéral, Rev. neurol. 1:921, 1929.

——and van Bogaert, L.: Etude anatomoclinique d'un cas de syndrôme rigide, avec spasme de torsion, ibid. 1:941, 1929.

Léri, A.; Layani, F., and Weill, V.: Dystonies d'attitude, Rev. neurol. 1:916, 1929.

Mankowsky, B. N., and Czerny, L. I.: Zur Frage über die Heredität der Torsionsdystonie, Monatschr. f. Psychiat. u. Neurol. 72:165, 1929.

Marinesco, G., and Nicolesco, M.: Un cas anatomoclinique de dystonie contorsive spasmodique avec lésions du striatum et des centres sous-thalamiques, Rev. neurol. 1:973, 1929.

Roasenda, G.: Spasme de torsion dans les muscles du membre supérieur gauche dans une lacunaire, Rev. neurol. 1:959, 1929.

Zolotova, N.: Torsionsyndrom bei Kindern mit diplegischer Form der cerebralen Lähmung, Zentralbl. f. d. ges. Neurol. u. Psychiat. 51:329, 1929.

Brunschweiler, H.: Quelques considérations pathogéniques à propos d'un cas de spasme de torsion fruste, Schweiz. Arch. f. Neurol. u. Psychiat. 25:289, 1930.

Cudnow, E.: Zur Frage der Torsionsdystonie, Ztschr. f. Neuropat. 23:39, 1930.

Fracassi, T., and Marelli, F.: 5 Fälle von Torsionsspasmus, Zentralbl. f. d. ges. Neurol. u. Psychiat. 58:78, 1930.

Regensburg, I.: Zur Klinik des hereditären torsionsdystonischen Symptomkomplexes, Monatschr. f. Psychiat. u. Neurol. 75:323, 1930.

Stern, A.: Ueber Blickkrämpfe, speziell in einem seltenen Fall von Dystonia, Klin. Wchnschr. 2:1589, 1930.

von Hallervorden: Athetose mit eigenartigen anatomischem Befund, Zentralbl. f. d. ges. Neurol. u. Psychiat. 56:114, 1930.

Lafora, G. R.: Ein Fall von progressiver Muskeldystonie, Zentralbl. f. d. ges. Neurol. u. Psychiat. 54:722, 1930.

Dias, A. A.: Ueber einen Fall von chronischer Encephalitis mit eigenartigem klinischem und anatomischem Befund, Ztschr. f. d. ges. Neurol. u. Psychiat. 137:82, 1931.

Herz, E.: Die amyostatischen Unruheerscheinungen, Leipzig, Johann Ambrosius Barth, 1931.

Luethy, F.: Ueber die hepato-lenticuläre Degeneration, Deutsche Ztschr. f. Nervenh. 123:101, 1931.

Ramos Fernández, R.: Espamo de torsión, Pediat. español. 20:281, 1931.

Seidemann, H.: Torsionsdystonie beim Kinde, Zentralbl. f. d. ges. Neurol. u. Psychiat. 58:866, 1931.

Vizioli, F.: Sindrome Wilsoniana atipica con spasmo di torsione, Riv. di neurol. 4:768, 1931.

Budde, O.: Zur Klinik der Torsionsdystonie; Casuistischer Beitrag, Monatschr. f. Kinderh. 54:398, 1932.

Dubitscher, F.: Ueber einem Fall mit hyperkinetisch-dystonischem Syndrom, Deutsche Ztschr. f. Nervenh. 127:133, 1932.

Garland, H. G.: Torsion Spasm (Dystonia Lenticularis) with Case Report, J. Neurol. & Psychopath. 12:193, 1932.

Jakob, A.: Zur Frage der nosologischen und lokalisatorischen Auffassung der torsionsdystonischen Krankheitserscheinungen, Deutsche Ztschr. f. Nervenh. 124:148, 1932.

Laruelle and Divry: Un cas de spasme de torsion (dysbasie lordotique), J. de neurol. et de psychiat. 32:495, 1932.

Rakonitz, E.: Ein Fall von exogener Hemitorsionsdystonie, Deutsche Ztschr. f. Nervenh. 129:43, 1932.

Saegesser, M.: Torticollis spastica, Mitt. a. d. Grenzgeb. d. Med. u. Chir. 42:633, 1932.

Schmitt, W., and Scholz, W.: Klinischer und pathologisch-anatomischer Beitrag zur Torsionsdystonie, Deutsche Ztschr. f. Nervenh. 126:53, 1932.

Foerster, O.: Mobile Spasm of the Neck Muscles and Its Pathological Basis, J. Comp. Neurol. 58:725, 1933.

Noble de Mello, A. L., and Quintanilha, F.: Dystonie von lokalisierter Drehung, Zentralbl. f. d. ges. Neurol. u. Psychiat. 69:72, 1933.

Agostini, C.: Sopra un caso di spasmo di torsione in encefalitica epidemica cronica (Nofa clinica ed anatomo-patologica), Riv. di pat. nerv. 43:440, 1934.

Quadfasel, F., and Krayenbühl, H.: Ueber Haltungsstörungen und ihre Beeinflussbarkeit: Eine klinische Untersuchung bei Kranken mit Torticollis spasticus mobilis, Monatschr. f. Psychiat. u. Neurol. 88:39, 1934.

Bernstein, S.: Ein Fall von Torsionskrampf, Wien. klin. Wchnschr. **25**:1567, 1912.

Bregman, L. E.: Zur Kenntnis der Krampfzustände des jugendlichen Alters, Neurol. Centralbl. **31**:885, 1912.

Fränkel, J.: Dysbasia Lordotica Progressiva, Dystonia Musculorum Deformans-Tortipelvis, J. Nerv. & Ment. Dis. **39**:361, 1912.

Abrahamson, I.: A Case of Dystonia Musculorum Deformans, J. Nerv. & Ment. Dis. **40**:38, 1913.

Bonhoeffer, K.: Fall von Torsionsspasmus, Neurol. Centralbl. **32**:137, 1913.

Bregman, L. E.: Ein Fall von Torsionsspasmus. abstracted, Jahresb. u. d. Leistung. d. Neurol. u. Psychiat. **17**:880, 1913.

Spiller, W. G.: A Case of Dystonia Musculorum Deformans, J. Nerv. & Ment. Dis. **40**:529, 1913.

Beling, C. C.: A Case of Dystonia Musculorum Deformans, J. Nerv. & Ment. Dis. **41**:148, 1914.

Haenisch: Progressiver Torsionsspasmus, Neurol. Centralbl. **33**:69, 1914.

Kroll, M.: Fall von "doppelter Athetose," Ztschr. f. d. ges. Neurol. u. Psychiat. **9**:197, 1914.

Seelert: Differentialdiagnose der Hysterie und des progressiven Torsionsspasmus, Neurol. Centralbl. **33**:988, 1914.

Biach: Ein Fall von "Dystonia musculorum deformans," Neurol. Centralbl. **34**:654, 1915.

Climenko, H.: A Case of Dystonia Musculorum Progressiva, J. Nerv. & Ment. Dis. **42**:167, 1915.

Diller, T., and Wright, G. J.: Dystonia Musculorum Deformans with Report of a Case, J. Nerv. & Ment. Dis. **43**:337, 1916.

Hunt, J. R.: The Progressive Torsion Spasm of Childhood (Dystonia Musculorum Deformans), J. A. M. A. **67**:1430 (Nov. 11) 1916.

Patrick, H. T.: Dystonia Musculorum or Tic, J. Nerv. & Ment. Dis. **44**:63, 1916.

Sterling, W.: Ein Fall von progressivem Torsionsspasmus, abstracted, Jahresb. u. d. Leistung. d. Neurol. u. Psychiat. **20**:766, 1916; cited by Mendel (1919).

Dercum, F. X.: A Case of Anomalous Torsion Spasm, J. Nerv. & Ment. Dis. **45**:420, 1917.

Hallock, F. M., and Frink, H. W.: Case of Dystonia Musculorum, J. Nerv. & Ment. Dis. **45**:348, 1917.

Weisenburg, T. H.: A Case of Unusual Torsion Spasm with Facial Movement, J. Nerv. & Ment. Dis. **45**:254, 1917.

Keschner, M.: Dystonia Musculorum Deformans, J. Nerv. & Ment. Dis. **47**:103, 1918.

Kramer: Torsionsspasmus-ähnliches Bild beim Erwachsenen, Neurol. Centralbl. **37**:221, 1918.

Thomalla, C.: Ein Fall von Torsionsspasmus mit Sectionsbefund, Ztschr. f. d. ges. Neurol. u. Psychiat. **41**:311, 1918.

Mendel, K.: Torsionsdystonie, Monatschr. f. Psychiat. u. Neurol. **46**:309, 1919.

Abrahamson, I.: Presentation of Cases of Familial Dystonia Musculorum of Oppenheim, J. Nerv. & Ment. Dis. **51**:451, 1920.

Collier, J.: Case of Torsion Dystonia, Proc. Roy. Soc. Med. **14**:12, 1920.

Frauenthal, H. W., and Rosenheck, C. H.: Dystonia Musculorum Deformans, J. Nerv. & Ment. Dis. **52**:134, 1920.

Spiller, W. G.: Acquired Double Athetosis (Dystonia Lenticularis), Arch. Neurol. & Psychiat. **4**:370 (Oct.) 1920.

Taylor, E. W.: Dystonia Lenticularis (Dystonia Musculorum Deformans), Arch. Neurol. & Psychiat. **4**:417 (Oct.) 1920.

Dawidenkow, S. N., and Zolotowa, N. A.: Eine Familie mit Torsionsspasmus, Mitt. Staatl. Univ. Baku **1**: 151, 1921; abstracted, Zentralbl. f. d. ges. Neurol. u. Psychiat. **31**:432, 1921.

Flater, A.: Ein Fall von Torsionsdystonie, Ztschr. f. d. ges. Neurol. u. Psychiat. **69**:27, 1921.

Price, G. E.: The Simultaneous Occurrence of Dystonia Lenticularis in Twins, Arch. Neurol. & Psychiat. **5**:768 (June) 1921.

Wimmer, A.: Etudes sur les syndromes extrapyramidaux: Spasme de torsion progressif infantile, Rev. neurol. **37**:952, 1921.

Cassirer, R.: Halsmuskelkrampf und Torsionsspasmus, Klin. Wchnschr. **1**:53, 1922.

Ewald, G.: Das dystonische Syndrom, München. med. Wchnschr. **69**:264, 1922.

Fossey, H.: A Case of Dystonia Musculorum with Remarkable Familial History, New York M. J. **116**:329, 1922.

Jacob, C.: Beitrag zur Kasuistik der Erkrankungen mit amyostatischem Symptomenkomplex, Arch. f. Psychiat. **65**:540, 1922.

Patrick, H. T.: A Case of Dystonia Musculorum Deformans, Arch. Neurol. & Psychiat. **7**:541 (April) 1922.

Pollock, L. V.: Some Diseases with Increased Movements (Dystonias), Internat. Clin. **1**:67, 1922.

Rosenthal, C.: Die dysbatisch-dysstatische Form der Torsionsdystonie, Arch. f. Psychiat. **66**:445, 1922.

Wartenberg, R.: Demonstration eines Falles von Torsionsdystonie, Zentralbl. f. d. ges. Neurol. u. Psychiat. **30**:80, 1922.

Wechsler, I. S., and Brock, S.: Dystonia Musculorum Deformans with Especial Reference to a Myostatic Form and the Occurrence of Decerebrate Rigidity Phenomena, Arch. Neurol. & Psychiat. **8**:538 (Nov.) 1922.

Yawger, N. S.: A Patient with Dystonia Musculorum Deformans, Arch. Neurol. & Psychiat. **7**:144 (Jan.) 1922.

Margaretten, I.: Case of Dystonia with Athetoid Features, Arch. Neurol. & Psychiat. **10**:709 (Dec.) 1923.

Richter, H.: Beiträge zur Klinik und pathologischen Anatomie der extrapyramidalen Bewegungsstörungen, Arch. f. Psychiat. **67**:226, 1923.

Rosenthal, C.: Torsionsdystonie und Athetose double, Arch. f. Psychiat. **68**:1, 1923.

Solomon, H. C.: Two Cases of Dystonia Lenticularis, Arch. Neurol. & Psychiat. **9**:256 (Feb.) 1923.

Wartenberg, R.: Demonstration eines Falles von Torsionsdystonie, Arch. f. Psychiat. **67**:114, 1923.

Fraenkel, F.: Demonstration zum dystonischen Syndrom, Zentralbl. f. d. ges. Neurol. u. Psychiat. **36**: 254, 1924.

Prissmann, J.: Ein Fall von dysbatisch-dysstatischer Form der Torsionsdystonie, Ztschr. f. d. ges. Neurol. u. Psychiat. **88**:1, 1924.

DELIRIUM

I. ELECTROENCEPHALOGRAPHIC DATA

JOHN ROMANO, M.D., AND GEORGE L. ENGEL, M.D.[*]
CINCINNATI

Delirium is a term of many meanings. Literally it means "to go out of the furrow in ploughing," i. e., "to go off the track." We shall use it to describe a syndrome sometimes called the symptomatic psychosis, the toxic-infectious exhaustion state or psychosis associated with somatic disease. Essentially it is a more or less reversible psychotic episode appearing symptomatically during the course of an underlying physical disorder. Thus, it may occur in patients with no preexisting structural cerebral disease and may be associated with such conditions as drug intoxications, febrile states and cardiac and renal disease. It may also occur spontaneously or may be precipitated by the aforementioned factors in patients with preexisting structural cerebral disease.

Previous psychologic and clinical studies [1] have led us to formulate a principle of release for the explanation of the intellectual, emotional and motor regressive behavior of delirious patients. We have found the primary psychologic disturbance to be that of an increased fluctuation in the level of awareness. Further, we have accumulated data to illustrate the loss of ability to think in the abstract. In experimental and spontaneous situations, the emotional behavior of patients has been more understandable when interpreted in the light of a release of inhibiting or repressing factors. Similarly, the purposeless body movements have been interpreted as due to a release of higher cerebral function and a return of behavior to a lower order of integration. These observations have led us to consider the fundamental physiologic substratum of delirium. If the total behavior of the delirious patient may

be interpreted as due to a release from higher cerebral function, what evidence other than clinical and psychologic data may be presented to support such a hypothesis?

The sensitive metabolic needs of cerebral tissue, particularly of the cortex, are well known. Serious disturbances in functional integrity of the cortex seem likely in the course of the physiologic derangements associated with physical disease. These physiologic derangements may result ultimately in (1) disturbances of transportation of oxygen, dextrose and other essential foodstuffs to the brain or (2) an alteration of the essential intracellular integrity and metabolism of the brain or (3) a combination of the two.

Methods of study of cortical function in human beings are limited, but knowledge based on animal experimentation that the electrical activity of nerve tissue closely parallels its functional integrity opens the possibility of a similar approach to the study of the human cortex. The electroencephalograph offers a method of study of the electrical activity of the human cortex. Gerard and associates [2] have presented evidence to show that the electroencephalogram represents the synchronized electrical activity of the individual neurons. Major factors determining these neuron potentials are the metabolic status of the cell, the membrane charge and the nature of the surrounding fluid medium. They may be modified, but are not solely determined, by influent nerve impulses. Changes in the rate, form and, within limits, amplitude induced by applied agents may be interpreted in terms of the individual neuron beat. Regularity, on the other hand, may be more readily interpreted in terms of synchronization. There is further evidence to suggest that this synchrony may be controlled or enhanced by "pace-making" cells, which set off other cells. In human beings and in animals

1. Romano, J., and Coon, G. P.: Physiologic and Psychologic Studies in Spontaneous Hypoglycemia, Psychosom. Med. 4:283, 1942. Romano, J.; Engel, G. L., and Evans, L.: Studies of Delirium: III. Psychologic and Clinical Considerations, to be published.

2. Gerard, R. W.; Factors Influencing Brain Potentials, Tr. Am. Neurol. A. 62:55, 1936. Dubner, H. H., and Gerard, R. W.: Factors Controlling Brain Potentials in the Cat, J. Neurophysiol. 2:142, 1939. Libet, B., and Gerard, R. W.: Control of the Potential Rhythm of the Isolated Frog Brain, ibid. 2:153, 1939. Gerard, R. W., and Libet, B.: The Control of Normal and "Convulsive" Brain Potentials, Am. J. Psychiat. 96:1125, 1940.

Santangelo, G.: Contributo clinico alla conoscenza delle forme familiari della dysbasica lordotica progressiva, Gior. di psichiat. e di neuropat. **62**:52, 1934.

Beilin, V. A.: Genetische und klinische Analyse des Torsionssyndroms, Ztschr. f. d. ges. Neurol. u. Psychiat. **152**:126, 1935.

Munch-Petersen, C. J.: Beitrag zur Frage des pathologisch-anatomischen Substrats der Torsionsdystonie, Acta psychiat. et neurol. **10**:391, 1935.

Mendel, K.: Torsionsdystonie, in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1936, vol. 16, p. 848.

Zádor, J.: Le spasme de torsion: Parallèle de tableaux cliniques entre la race juive et les autres races, Rev. neurol. **66**:365, 1936.

Paulian, D., and Cardas, M.: Le spasme de torsion, Arch. de neurol. **1**:224, 1937.

Davison, C., and Goodhart, S. P.: Dystonia Musculorum Deformans: Clinicopathologic Study, Arch. Neurol. & Psychiat. **39**:939 (May) 1938.

Maspes, P. E., and Romero, A.: Spasmo di torsione con atetosi, Riv. di pat. nerv. **52**:1, 1938.

Gordin, R.: Case of Unilateral Torsion Dystonia: Clinicohistologic Study, J. Nerv. & Ment. Dis. **90**:344, 1939.

Benedek, L., and Rakonitz, E.: Heredopathic Combination of Congenital Deformity of Nose and of Myoclonic Torsion Dystonia, J. Nerv. & Ment. Dis. **91**:608, 1940.

Nielsen, F. M.: Autopsy in a Case of Dystonia Musculorum Deformans, Bull. Los Angeles Neurol. Soc. **6**:87, 1941.

Keschner, M.: Dyskinesias, in Tice, F.: Practice of Medicine, Hagerstown, Md., W. F. Prior Company, Inc., 1942, vol. 10, p. 307.

Herz, E.: Dystonia: I. Historical Review, Arch. Neurol. & Psychiat., this issue, p. 305.

manifested by sense deceptions, confabulation and motor restlessness, and underactivity, including somnolence and stupor, were common features of patients with severe disturbances.

B. *Electroencephalographic Methods.*—Electroencephalograms were taken each time the patient was studied psychologically. A two channel,[7] and later a three channel, ink-writing apparatus, constructed by Mr. Albert Grass, was used. Solder electrodes were placed on the frontal, parietal and occipital areas. Bipolar tracings were taken routinely from the left fronto-occipital, the right fronto-occipital, the transfrontal, the transparietal and the transoccipital leads. Other electrode combinations were used whenever indicated for exclusion of focal abnormalities. Tracings were taken from each area for a run of five minutes. Every precaution was observed to avoid the artefacts of sleep or movement. It is our belief that artefacts occur less frequently when the bipolar method is used. This is of practical importance in the study of disturbed patients. The patients were under constant surveillance of the operator, so that any movement could be recorded. Occasionally simultaneous records of eyeball potentials were taken to exclude movement of the eyes as a source of artefact.[8]

In the interpretation of the electroencephalogram, particular attention was directed to the progressive changes which occurred during the clinical course. The chief features considered were (1) frequency, (2) amplitude, (3) regularity and degree of organization, (4) paroxysmal features, (5) focal abnormalities and (6) wave form.

In order to demonstrate these progressive changes more quantitatively, a method of spectrum frequency analysis was devised. Frequency was selected as the variable for analysis, since data previously cited [2] have indicated that it is probably the most valuable index of the activity of individual neurons as influenced by such factors as metabolic states, membrane charge and nature of the surrounding mediums.

The method is described in detail elsewhere.[9] Briefly, it involved counting the number of waves in each one second interval for a total of three hundred seconds. A complete wave is one which returns at least 60 per cent of the way to the base line. For practical purposes it was found that the countable waves ranged in frequency from 1 to 12 per second, while the faster waves existed largely as low voltage irregular waves, which could not be accurately counted and hence were grouped together as low voltage fast activity. Low voltage fast waves superimposed on discrete, countable (1 to 12 per second) waves were ignored. When a given interval contained both countable waves and low voltage fast activity, the frequency which occupied the greater portion of that interval was arbitrarily taken as dominant.

Such an analysis yields a "spectrum" expressing the distribution of waves for one second intervals rather than that of true wavelengths—that is, the percentage of one second intervals containing 12 waves, 11 waves, etc., rather than the percentage of 12 per second waves, 11 per second waves, etc. It is obvious that sporadic waves faster or slower than the dominant frequency will be averaged with the more dominant frequency and hence will not be represented in the spectrum, although they may be obvious on inspection; this, however, does not obscure shifts in frequency, detection of which is the primary objective of the method.

With very regular records the error in this method is relatively insignificant. Under the same conditions, a rather consistently reproducible frequency spectrum can be obtained.[9] Observations on normal adults indicate that the normal records may be classified under two chief types, i. e., (1) records with 75 per cent or more 8 to 12 per second activity, with the remainder low voltage fast activity, and (2) predominantly low voltage fast activity, with small and varying amounts of 8 to 12 per second activity. It is unusual in our experience to find that a normal record contains more than 5 per cent 7 per second activity. Minimal variations in the dextrose, oxygen and carbon dioxide contents have been found to produce significant alterations in the frequency distributions of normal records.[9] With abnormal records, as the degree of irregularity increases, this method of analysis becomes less accurate, but for comparative purposes the error is more or less self limited, since the more irregular records are generally the more abnormal and the frequencies tend to shift to a large degree to the abnormally slow or the abnormally fast zones.

Spectrum analyses were performed at each examination. The left fronto-occipital tracing was utilized routinely unless focal differences were present. We utilized the fronto-occipital tracing because it represented a composite of the electrical activity of the major portion of the hemisphere. We were interested in examining the grosser features of cortical activity before embarking on a more detailed study of discrete cortical areas.

C. *Special Physiologic Studies.*—The routine laboratory tests pertinent to each patient's problem were carried out. In addition, certain special procedures were utilized. For patients with cardiac or pulmonary decompensation, the venous pressure, the circulation time (dehydrocholic acid), the vital capacity and the oxygen saturation of arterial blood were determined. Dextrose tolerance tests (0.5 Gm. of dextrose per kilogram of body weight introduced intravenously in 10 per cent solution in thirty minutes) were carried out on patients with Addison's disease and others with malnutrition associated with debility and chronic disease.

CLINICAL MATERIAL

Fifty-three patients were studied. The basic pathophysiologic factors underlying the delirious state were usually multiple, and probably cumulative, but in general the patients could be classified under the following disease categories: (1) acute or chronic cardiac decompensation, 15 patients; (2) acute or chronic pulmonary decompensation resulting from chronic asthma, bronchitis, emphysema or recurrent pneumonitis, 7 patients; (3) structural cerebral disease (atrophy, vascular degenerative changes and Sydenham's chorea [chorea minor]), 5 patients; (4) malnutrition and wasting due to chronic infection or neoplastic disease, 5 patients; (5) chronic alcoholism and delirium tremens, 5 patients, including 1 patient with Wernicke's encephalopathy (hemorrhagic superior polioencephalitis); (6) toxic states due to acute infections, 2 patients, including 1

7. Dr. Hallowell Davis loaned the two channel electroencephalograph which was used in the early experiments.

8. Lyman, R. S.: Eye Movements in the Electroencephalogram, Bull. Johns Hopkins Hosp. 68:1, 1941.

9. Engel, G. L.; Romano, J.; Ferris, E. B.; Webb, J. P., and Stevens, C. D.: A Simple Method of Determining Frequency Spectrums in the Electroencephalogram: Observations on Physiologic Variations in Dextrose, Oxygen, Posture and Acid-Base Balance on the Normal Electroencephalogram, Arch. Neurol. & Psychiat. 51:134 (Feb.) 1944.

striking changes in the electroencephalogram resulting from anoxia, hypoglycemia, acapnia, alkalosis and electrolytic imbalance have been demonstrated.[3] Other investigations have clarified the effects of drugs which alter consciousness.[4] Clinically a number of studies of the electroencephalographic changes in patients with diffuse inflammatory, traumatic or degenerative diseases of the brain [5] have been carried out. In addition, there are reports of electroencephalographic changes in patients with disease not directly affecting the central nervous system, such as Addison's disease and pulmonary and cardiac insufficiency.[6] Unfortunately, in many of these clinical studies the psychologic data, even

---

3. Sugar, O., and Gerard, R. W.: Anoxia and Brain Potentials, J. Neurophysiol. **1**:558, 1938. Davis, H., and Davis, P. A.: The Electrical Activity of the Brain: Its Relation to Physiological States and to States of Impaired Consciousness, A. Research Nerv. & Ment. Dis., Proc. **19**:50, 1939. Hoagland, H.; Rubin, M. A., and Cameron, D. E.: The Electroencephalogram of Schizophrenics During Insulin Hypoglycemia and Recovery, Am. J. Physiol. **120**:559, 1937. Gibbs, F. A.; Williams, D., and Gibbs, E.: Modification of the Cortical Frequency Spectrum by Changes in Carbon Dioxide, Oxygen, and Blood Sugar, J. Neurophysiol. **3**:49, 1940.

4. (a) Drohocki, Z., and Drohocka, J.: Etude electroencephalographique de la localisation pharmacologique des narcotiques, Arch. internat. de. pharmacodyn. et de thérap. **62**:265, 1939. (b) Rubin, M. A., and Freeman, H.: Brain Potential Changes in Man During Cyclopropane Anesthesia, J. Neurophysiol. **3**:33, 1940. (c) Beecher, H. K., and McDonough, F. K.: Cortical Action Potentials During Anesthesia, ibid. **2**:289, 1939. (d) Hoagland, H.; Himwich, H. E.; Campbell, E.; Fazekas, J. F., and Hadidian, Z.: Effects of Hypoglycemia and Pentobarbital Sodium on Electrical Activity of Cerebral Cortex and Hypothalamus, ibid. **2**:276, 1939. (e) Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: Effect on the Electroencephalogram of Certain Drugs Which Influence Nervous Activity, Arch. Int. Med. **60**:154 (July) 1937.

5. (a) Lindsley, D. B., and Cutts, K. K.: Clinical and Electroencephalographic Changes in a Child During Recovery from Encephalitis, Arch. Neurol. & Psychiat. **45**:156 (Jan.) 1941. (b) Jasper, H. H.; Kershman, J., and Elvidge, A.: Electroencephalographic Studies of Injury to the Head, ibid. **44**:328 (Aug.) 1940. (c) Williams, D.: The Electroencephalogram in Acute Head Injuries, J. Neurol. & Psychiat. **4**:107, 1941; (d) The Electroencephalogram in Chronic Post-Traumatic Cases, ibid. **4**:131, 1941; (e) Abnormal Cortical Potentials Associated with High Intracranial Pressure, Brain **62**:321, 1939. (f) Finley, K. H.; Rose, A. S., and Solomon, H. C.: Electroencephalographic Studies on Neurosyphilis, Arch. Neurol. & Psychiat. **47**:718 (May) 1942.

6. Engel, G. I., and Margolin, S. G.: Neuropsychiatric Disturbances in Internal Disease: Metabolic Factors and Electroencephalographic Correlations, Arch. Int. Med. **70**:236 (Aug.) 1942. Hoffman, C. W. C.; Lewis, R. A., and Thorn, G. W.: The Electroencephalogram in Addison's Disease, Bull. Johns Hopkins Hosp. **70**:335, 1942.

---

as they related to the level of consciousness, are incomplete.

METHODS

A. *Psychologic Methods.*—A detailed report of the intellectual and emotional behavior of delirious patients will be found in another report.[1b] In this paper we shall enumerate the psychologic methods used principally to determine the fundamental psychologic disturbance, i. e., the increased fluctuation of the level of awareness.

After a traditional examination of the mental status was completed, with particular attention to the sensorium, each patient was presented with an additional battery of clinical psychologic tests. These included:

1. Tests for attention
   (a) Number and letter series
   (b) Serial subtraction
2. Tests of memory
   (a) Five objects test
   (b) Retention of digits, forward and backward
   (c) Syllable span
   (d) Fire story
   (e) Word pairs
   (f) Story recall (confabulation)
3. Arithmetical tests
4. Tests of capacity for abstract thinking
   (a) Group arrangement
   (b) Goldstein (Kohs) blocks
   (c) Proverbs and fables

With this method of examination we encountered a significant number of patients in the medical wards who fulfilled the essential criteria of delirium as defined by us but who had not been recognized as delirious by the medical attendants. The disturbance of awareness in these patients was demonstrated chiefly by testing, as many did not spontaneously express the anxiety, motor restlessness, disturbed thinking and sense deceptions characteristic of the more obviously disturbed patients. These patients were not necessarily experiencing milder degrees of delirium. On the contrary, such patients were apt to become somnolent and stuporous without a preceding phase of excitement.

The tests were repeated from time to time during the course of the delirium. It is to be noted that the limitations of the methods used were understood by us and were employed to indicate changes of clinical significance. The changes observed could not be explained by the patient's having learned the material, as the disturbance in memory and the magnitude of changes made this unlikely.

For gross comparison the disturbances in awareness were classified as mild, moderate and pronounced. With mild disturbance in the level of awareness the patient was generally correctly oriented but tended to make errors in serial subtraction and in the arithmetical tests, manifested memory defects and generally had some difficulty in abstract thinking. With a moderate disturbance the subject revealed some errors in orientation and gross errors in attention, memory and capacity for abstract thinking, but usually was able more or less to complete the tests. The disturbance was classified as pronounced when the patient had great difficulty in comprehending the nature of the examination and could not sustain attention. Such patients usually were disoriented to a conspicuous degree and were unable to complete the tests. Overactivity, as

CASE 3.—*H. C., a boy aged 13 yr. Acute glomerulonephritis; epilepsy (?). Duration of delirium before first examination, two days. Admission, Feb. 11, 1942.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
2/12	Severe	IV (fig. 3)	Two convulsions on preceding day; blood pressure 160/110; proteinuria, 4+; nonprotein nitrogen of blood 41 mg. per 100 cc.; facial edema 1+
2/16	Mild	III-II	Dramatic clinical improvement; proteinuria 2+; nonprotein nitrogen of blood 39 mg. per 100 cc.; wave and spike electroencephalographic pattern during hyperventilation
2/23	None	I*	Proteinuria 1+; wave and spike pattern still present on hyperventilation
3/13	None	I*	Proteinuria 1+; nonprotein nitrogen of blood 41 mg. per 100 cc.; wave and spike pattern still present
3/24	None	I*	Proteinuria 1+

* In this case, stage I of the electroencephalographic pattern was complicated by the paroxysmal, spontaneous appearance of slow waves, in addition to the wave and spike pattern following hyperventilation. We interpreted this as evidence of an epileptic predisposition. The clinical history tended to confirm this. During recovery, the record became progressively more regular, and the percentage of normal frequencies increased from zero to 75 per cent.

CASE 4.—*A. P., a woman aged 74. Anemia, of unknown cause. Duration of delirium before first examination unknown. Admission, April 6, 1942.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
4/9	Moderate	II	Hemoglobin content 2.5 Gm. per 100 cc., red blood cells 630,000 and white cells 7,000 per cu. mm.; oxygen content of arterial blood 5.3 volumes %; nonprotein nitrogen of blood 58 mg. per 100 cc.
4/11	Mild	I to normal	After transfusion of 1,000 cc. of blood, hemoglobin content 5.8 Gm. per 100 cc. and red cells 1,660,000 per cu. mm.; oxygen content of arterial blood 9.8 volumes %
5/1	Normal state	Electroencephalogram not made	After transfusion of 1,500 cc. of blood, hemoglobin content 7.2 Gm. per 100 cc. and red cells 2,010,000 per cu. mm.

CASE 5.—*E. D., a woman aged 67. Pernicious anemia; combined system disease. Duration of delirium before first examination, over three weeks. Admission, Dec. 26, 1941.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
1/6	Pronounced	V-IV	Hemoglobin 7.12 Gm. per 100 cc.; red cells 2,090,000 per cu. mm.; reticulocyte count 35 %; intramuscular injections of 1 cc. of liver for ten days
4/17	Mild	Normal pattern	Hemoglobin 13 Gm. per 100 cc.

CASE 6.—*J. N., a man aged 36. Diabetes mellitus, with acidosis. Duration of delirium before first examination, two days. Admission, Jan. 9, 1942.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
1/10	Mild	II	In preceding 16 hr. patient received 200 units insulin and 3,000 cc. of 5% dextrose in saline solution; carbon dioxide content of arterial blood 40.9 volumes %; blood sugar, 161 mg. per 100 cc.
1/12	None	I to normal	No chemical evidence of acidosis or hyperglycemia

CASE 7.—*H. O., a man aged 62. Typhus. Duration of delirium before first examination, one week. Admission, April 23, 1942.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
4/25	Moderate	II	Patient improving; temperature 103 F.; cerebrospinal fluid pressure 1.0 mm. of water; 10 white cells per cu. mm.; total protein 53 mg. per 100 cc.
4/30	None	Normal pattern	Patient afebrile 6 days; decided clinical improvement

CASE 8.—*H. H., a man aged 45. Vascular degenerative cerebral disease; carbon monoxide encephalopathy(?). Duration of delirium before first examination, five weeks. Admission, Feb. 8, 1942.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
2/27	Severe	V	Diagnostic problem: degenerative or inflammatory disease (?)
3/9	Mild to None	I	Patient gradually improved; residual weakness on right side; rigidity; tremor

CASE 9.—*E. M., a woman aged 47. Epilepsy; diphenylhydantoin intoxication (?). Duration of delirium before first examination unknown. Admission, Feb. 26, 1942.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
2/28 10:30 a.m.	Moderate to mild	II (fig. 2)	Psychomotor seizure at 9 a.m.; diphenylhydantoin intoxication (?); nystagmus
2/28 12 m.	Pronounced	IV	Psychomotor seizure at 11:30 a.m.
3/3	Mild	I	No further seizures
4/9	None	Normal pattern	No further seizures; patient receiving phenobarbital therapy

CASE 10.—*J. S., a man aged 21. Chronic ulcerative colitis. Duration of delirium before first examination unknown. Admission, September 1941.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
10/6	Mild	I	Bloody diarrhea; fever; loss of weight for two to three months
10/15	None	Normal pattern	Decrease in fever, diarrhea and evidence of toxicity

patient with typhus (Brill's disease); (7) malignant hypertension, acute glomerulonephritis or uremia, 4 patients; (8) severe anemia, 3 patients, 2 of whom had pernicious anemia; (9) Addison's disease, 3 patients; (10) jaundice, 2 patients, the condition of 1 being due to biliary obstruction and that of the other to hepatic degeneration; (11) acidosis associated with diabetes, 1 patient, and (12) epilepsy, 1 patient.

RESULTS

Electroencephalographic abnormalities were observed in the records of all patients who had disturbances of awareness. These changes were diffuse in the tracings of all but 3 patients for whom other data confirmed focal cerebral involvement. The character of the electroencephalographic change appeared to be independent of the specific underlying disease process in all cases except those of the 3 patients with Addison's disease, which will be discussed in detail. A more significant relation was found between the electroencephalographic changes and the intensity, duration and reversibility of the noxious factors as modified by the basic physiologic status of the body, particularly that of the central nervous system prior to the experience of delirium. These changes were observed to be reversible to the extent to which the clinical delirium was reversible.

When the electroencephalograms were analyzed as a group and individually during the patient's recovery or as missing metabolic requirements were supplied, the varieties of changes were found to constitute various stages of a continuous process. For purposes of convenience we have arbitrarily classified these electroencephalographic changes under five categories: It must be emphasized that the divisions are arbitrary and that the various stages represent phases of a continuous process. They are enumerated in the order of their increasing severity (fig. 1).

Stage I: Predominance of normal and regular frequencies, but with a small amount of regular and irregular slow frequencies (5 to 7 per second). There is generally some decrease in regularity of the record as a whole.

Stage II: A further decrease in regularity of the entire record, which now contains only a moderate amount of normal, regular frequencies. There is an increase in both low voltage fast activity and regular and irregular slow (4 to 7 per second) frequencies.

Stage III: Predominant low voltage fast activity with some regular and irregular slow frequencies (3 to 6 per second) and relatively little activity of the normal frequency range.

Stage IV: Completely disorganized, irregular record, with a dominant slow frequency (2 to 7

per second), varying small amounts of low voltage fast activity and no recognizable alpha activity (8 to 12 per second). At this stage groups of high voltage very slow waves (½ to 3 per second) frequently recur in a rhythmic fashion. Low voltage fast activity is sometimes superimposed on these slow waves.

Stage V: Fairly regular, moderately high voltage slow activity (3 to 7 per second), with few or no normal frequencies.

Stages III, IV and V are not influenced by the subject's opening or closing the eyes.

As stated previously, stages I to V represent graduations of a continuous process. However, stage V represents a more or less stabilized, and often irreversible, progression from stage IV. It suggests reorganization or stabilization of the electrical pattern at a lower energy level. The correlation between the clinical course and the electroencephalographic changes may best be demonstrated by the following classification of our material.

Group I, Twelve patients showed complete, or nearly complete, restoration to normal of the clinical behavior and of the electroencephalographic pattern. The following tabulations indicate the underlying physical disease, the degree of psychologic disturbance and the stage of electroencephalographic abnormality during the period of observation.

CASE 1.—*M. R., a woman aged 28, Acute and chronic alcoholism: Wernicke's syndrome. Duration of delirium before first examination, eight days. Admission, Jan. 1, 1942.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
1/2	Pronounced; patient semistuporous	IV (fig. 4)	Parenteral administration of fluids; tube feedings; no supplemental
1/5	Pronounced; Korsakoff syndrome	IV-III	vitamins
1/7	Pronounced; Korsakoff syndrome	III	
1/12	Moderate	II	
1/16	Mild	I	
2/25	None	Normal pattern	

CASE 2.—*K. T., a woman aged 61. Hypertensive heart disease: congestive heart failure. Duration of delirium before first examination, two weeks. Admission, Dec. 16, 1941.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
12/29/41	Severe	IV	Circulation time 34 sec.
1/5/42	Moderate	II	Circulation time 30 sec; venous pressure 20 mm. of water
1/7	Mild	I	
4/17	None	Normal pattern	No congestive heart failure

Course of Illness.—First Examination (Jan. 2, 1942): The patient was semistuporous and muttered incoherently. No formal status could be established. The results of neurologic examination were the same as those previously noted.

Second Examination (January 5): The patient had received intravenous injections of dextrose in isotonic solution of sodium chloride and then tube feedings, but no supplemental vitamins were given. She had begun to improve spontaneously on the second day of hos-

STAGE I

A)CASE NO.12 J.T. ARTERIOSCLEROTIC HEART DISEASE; CONGESTIVE FAILURE 9/26/41

B)CASE NO.2 K.T. HYPERTENSIVE HEART DISEASE; CONGESTIVE FAILURE 1/7/42

STAGE II

A) CASE NO.4 A.P ANEMIA, ETIOLOGY UNKNOWN 4/9/42

B) CASE NO.7 H.O. BRILL'S DISEASE (ENDEMIC TYPHUS) 4/25/42

STAGE III

A)CASE NO.18 J.M. CHRONIC BRONCHITIS, ASTHMA, EMPHYSEMA, PULMONARY FIBROSIS 11/7/41

B)CASE NO.37 F.A. CHRONIC BRONCHITIS, ASTHMA, EMPHYSEMA 2/19/42

STAGE IV

A)CASE NO.36 R.B. HYPERTENSIVE HEART DISEASE; CONGESTIVE FAILURE, HEART BLOCK 3/24/42

B) CASE NO.38 M.P. CIRRHOSIS OF LIVER, CHOLEMIA 1/19/42

STAGE V

A) CASE NO. 5 E.D. PERNICIOUS ANEMIA; COMBINED SYSTEM DISEASE 1/6/42

B) CASE NO. 23 G.S. ARTERIOSCLEROTIC HEART DISEASE; CONGESTIVE FAILURE 9/24/41

Fig. 1.—The five electroencephalographic stages (see text for description). Each stage is illustrated by samples from 2 cases.

The electroencephalogram was irregular throughout, with large, high voltage slow waves and superimposed, irregular, low voltage fast activity. There was no normal activity. This pattern represents stage IV (fig. 4).

pitalization. Ocular movements were now normal, and rigidity had disappeared.

The patient was no longer stuporous but was completely disoriented; she misidentified people, confabulated freely and showed marked fluctuation of attention.

CASE 11.—*J. L., a man aged 49. Hypertensive heart disease; chronic alcoholism; nutritional deficiency; congestive heart failure. Duration of delirium before first examination, more than two weeks. Admission, March 6, 1942.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
3/16	Mild	II-I	Increasing delirium with sense deceptions, but notable improvement in preceding 4 days; venous pressure 120 mm. of water; circulation time 18 sec.
3/26	None	Normal fast pattern*	Compensated heart disease

* The last electroencephalogram showed predominantly fast, 13 to 19 per second activity, with an amplitude of 5 to 20 microvolts. We considered this the patient's normal pattern.

CASE 12.—*J. T., a man aged 74. Arteriosclerotic heart disease; congestive heart failure. Duration of delirium before first examination unknown. Admission, Sept. 20, 1942.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
9/26	Mild	I	Minimal evidences of congestive heart failure; circulation time 22 sec.; confusion greatly decreased by this time
9/30	None	I to normal pattern	No evidence of congestive heart failure

From the protocals it may be seen that at the time of initial study 4 patients showed stage IV electroencephalograms, 2 patients stage V electroencephalograms, 4 patients stage II electroencephalograms and 2 patients stage I electroencephalograms. The diagnoses are indicated in italics. The 6 patients with stage IV or stage V electroencephalograms were all greatly confused at the time of initial examination. The more irregular and disorganized slow activity (stage IV) was associated with delirium of more acute onset (of two weeks' duration or less), while the 2 patients with the regular but very slow rhythm had been delirious for three to five weeks or longer. The electroencephalograms of all the patients, however, showed complete, or almost complete, reversibility to a normal pattern. The remaining 6 patients with stage I or stage II electroencephalograms showed only mild to moderate disturbances in the level of awareness. At least 2 patients (J. L., case 11, with chronic alcoholism and congestive heart failure, and H. O., case 7, with typhus) were recovering at the time of the first examination, and probably the electroencephalograms would have manifested more conspicuous changes if they had been taken earlier.

E. M. (case 9), with epilepsy, offered an unusual opportunity for observation of the electroencephalogram and the mental status preced-

ing and immediately after two typical psychomotor seizures. Two minutes after the second seizure, during which the patient sat up, stared, turned to the right and showed rhythmic chewing motions, she was greatly confused, and the electroencephalogram showed a dominantly slow (3 to 7 per second) and moderately irregular record, with many high voltage 3 per second waves. This record was indistinguishable from that for other patients with severe delirium except that the individual waves were somewhat more regular and more nearly sinusoidal. When the patient was examined again, after a six week period of freedom from seizures, the electroencephalogram was entirely normal, showing 84 per cent 8 to 10 per second activity, 15 per cent low voltage fast activity and only 1 per cent 7 per second activity (fig. 2).

One other patient (H. C., case 2, a boy aged 13 years, with acute glomerulonephritis) probably also had epilepsy. The onset of his delirium was accompanied by convulsions, and the electroencephalograms taken during recovery, while showing 75 per cent normal frequencies, still revealed paroxysmal groups of slower (6 to 7 per second) waves appearing spontaneously and a wave and spike pattern on hyperventilation. Again, the records taken during maximal confusion were undistinguishable from those of other extremely delirious patients (fig. 3).

The following case is illustrative of group I.

CASE 1.— M. R., a saleswoman aged 28, with a history of chronic addiction to alcohol for five years or more, noticed painful calves and burning of the feet three to four months before her admission to the hospital; this condition had been getting worse. One week before admission she embarked on a drinking spree and quickly became acutely intoxicated. She then showed increasing disturbance in awareness, tremor, overactivity and sensory deceptions, and three days later she lapsed into stupor. She was admitted to the Peter Bent Brigham Hospital in this state, on Jan. 1, 1942.

Examination.—The patient was somewhat obese. She was semistuporous and showed little spontaneous activity. She responded to painful stimuli by grimacing and mumbling and with aimless movements of the extremities. Movements of the eyes were limited and incoordinated. The pupils reacted to light. There was occasional rigidity on passive movements of the extremities. The tendon reflexes were overactive. The abdominal reflexes could not be elicited. The rest of the physical examination revealed nothing pertinent except evidences of dehydration.

Examination of the cerebrospinal fluid revealed normal pressure and dynamic state, no cells and a total protein content of 43 mg. per hundred cubic centimeters. Examination of the urine, blood and stools revealed nothing abnormal.

Fifth Examination (January 16): The patient was now correctly oriented; attention was sustained; memory was intact in all categories; ability for abstract thinking was good, and she no longer confabulated. The spontaneous content of thought seemed normal.

The electroencephalogram was now regular, with 61 per cent normal activity, 8 per cent 6 to 7 per second activity and 31 per cent low voltage fast activity. This record represented stage I.

Sixth Examination (February 15): The patient had been out of the hospital for one month and had been back at her work for two weeks. She had not resumed drinking. Examination of the mental status revealed no residual defects.

The electroencephalogram was now an unequivocally normal record, consisting of 89 per cent regular, 8 to 12 per second activity.

Group 2.—Ten patients showed partial restoration to normal of clinical and electroencephalographic disturbances. Some of these patients may belong to the first group, but we were unable to follow them long enough to establish evidence of complete restoration.

CASE 13.—*A. C., a woman aged 55. Hypertensive heart disease; congestive heart failure. Duration of delirium before first examination, three weeks. Admission, April 25, 1942.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
4/27	Severe	IV	Venous pressure 150 mm. of water, with increase to 200 mm. of water on compression of liver; circulation time 26 sec.; oxygen saturation of arterial blood 80%
5/7	Severe to moderate	III-IV	Diminished signs of heart failure

CASE 14.—*L. S., a man aged 60. Arteriosclerotic heart disease; chronic congestive heart failure. Duration of delirium before first examination, four weeks plus. Admission, Jan. 9, 1942.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
1/20	Mild to moderate	III (fig. 5)	Venous pressure 180 mm. of water, with rise to 230 mm. of water on compression of liver; circulation time 53 sec.; oxygen saturation of arterial blood 96%
1/24	Severe	IV	Degree of congestive failure unchanged; venous pressure 180 mm. of water, with rise to 250 mm. of water on compression of liver; circulation time, no end point
1/26	Moderate	IV	Venous pressure 140 mm. of water, with rise to 180 mm. of water on compression of liver; circulation time 49 sec.
2/12	Mild	II-I	No clinical evidence of congestive heart failure; patient ready to be discharged

CASE 15.—*W. F., a woman aged 54. Acute coronary occlusion; congestive heart failure. Duration of delirium before first examination, three to four weeks. Admission, Sept. 16, 1941.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
10/2	Severe	III-IV	Venous pressure 180 mm. of water; circulation time 43 sec.; Cheyne-Stokes respiration
10/23	Mild	II-I	Degree of congestive failure much diminished; normal respiration; venous pressure 40 mm. of water, with no rise on compression of liver; circulation time 33 sec.; oxygen saturation of arterial blood 95.8%

CASE 16.—*M. D., a woman aged 65. Arteriosclerotic heart disease; congestive heart failure; auricular fibrillation. Duration of delirium before first examination, two weeks. Admission, Oct. 10, 1941.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
10/21	Moderate	II-III	Enlarged heart; bilateral hydrothorax; basal rales; improvement in patient's condition
10/27	Mild to moderate	I	Minimal evidence of heart failure

CASE 17.—*J. S., a man aged 45. Chronic alcoholism; malnutrition; malignant retroperitoneal tumor. Duration of delirium (intermittent) before first examination, one year. Admission, Jan. 27, 1942.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
2/27	Moderate to severe	V	Patient had been much more delirious but was responding to transfusions, high caloric diet and administration of supplemental vitamins
5/8	Moderate	I	Patient had greatly improved in home for convalescents; April 20 abdominal pain developed; laparotomy (5/4) revealed a malignant retroperitoneal tumor

CASE 18.—*J. M., a man aged 49. Chronic bronchitis, asthma, emphysema, pulmonary fibrosis; failure of right side of heart; secondary polycythemia.* Duration of delirium before first examination, one month. Admission, Nov. 3, 1941.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
11/6	Moderate	III	Intense cyanosis; oxygen saturation of arterial blood 56%; carbon dioxide content 59.8 volumes %
11/7	No tests	III	Oxygen saturation of arterial blood 50%; carbon dioxide content 56.4 volumes %
11/10	Mild	III-II	Oxygen saturation of arterial blood 71.4%; carbon dioxide content 53.2 volumes %
11/13	Mild	II	Oxygen saturation of arterial blood 84.3%; carbon dioxide content 53.9 volumes %

* The patient died at home some months later. Autopsy was not performed.

Memory and ability to think abstractly were notably deficient. She rambled on from one topic to another through vague associations, as in a dream. She now presented the picture of a typical Korsakoff psychosis. The electroencephalogram at this time showed chiefly irregular, low voltage fast activity, with persistence of some large, slow waves, and little, if any, normal activity. This record represented a transition to stage III.

nizable frequencies (24 per cent) in the normal range, which, however, were poorly organized. This record represented stage III.

Fourth Examination (January 12) : The patient was now much more alert and more correctly oriented. She stated that she felt as if she had just awakened from a long and disturbing dream. Attention was fair, and she was able to subtract serially, with some errors.
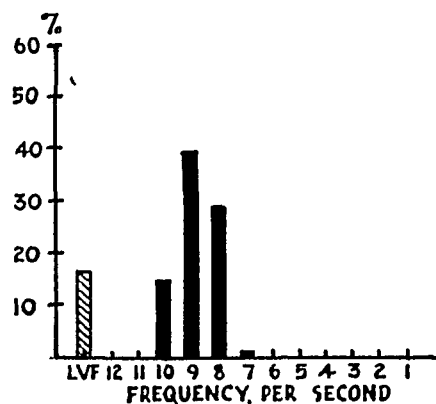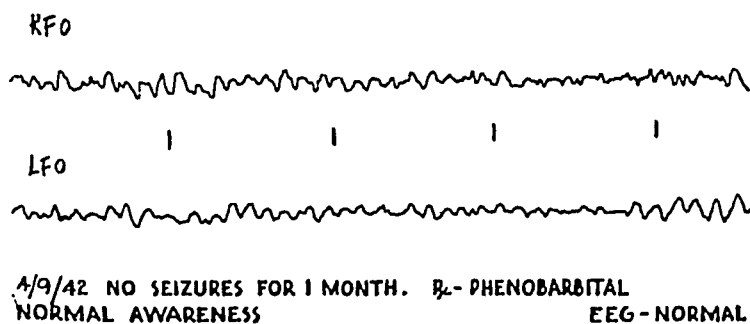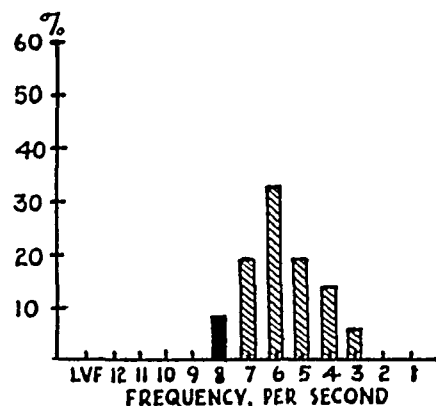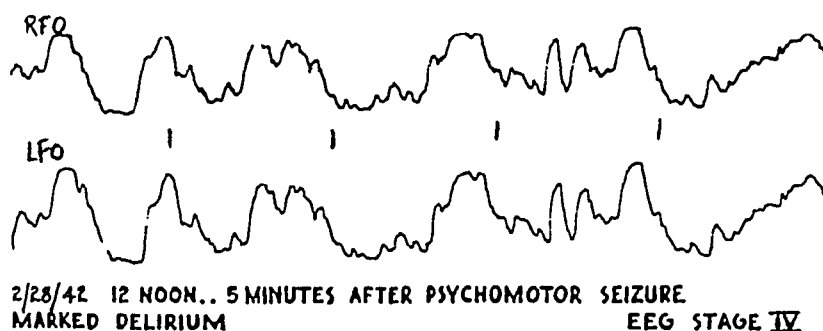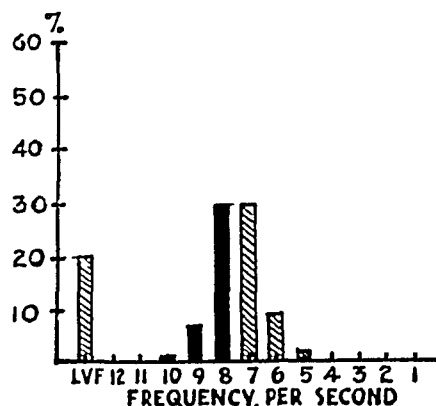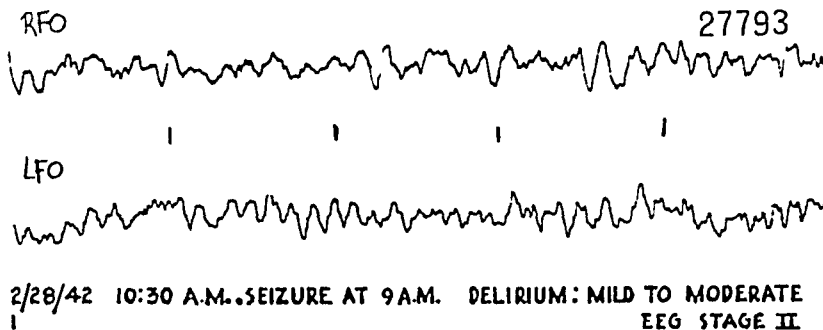
Fig. 2.—Electroencephalograms immediately before and after a psychomotor seizure.

The first electroencephalogram represented stage II and was taken during mild to moderate delirium one and a half hours after a typical psychomotor seizure and one and one-half hours before a second seizure. Five minutes after the second seizure confusion was severe and the electroencephalogram was of stage IV type. Six weeks later, after no seizures for one month and with adequate therapy, the electroencephalogram was normal, and there was no disturbance in awareness.

Third Examination (January 7) : The patient was still disoriented and confabulated freely. Attention and memory were defective. She read with many errors and was unable to comprehend or relate what she had read. She still recounted dreamlike experiences as though they were real.

The electroencephalogram was still irregular, with much low voltage fast activity, but with more recog-

Reading and memory for stories were much better, although she still confabulated moderately in filling in details. Interpretation of proverbs was fairly good.

The electroencephalogram showed beginning organization and regularity, with 49 per cent normal frequencies, mixed with some low voltage fast (33 per cent) activity and slow (5 to 7 per second) activity (19 per cent). This record represented stage II.

instance with severe disturbances of awareness. Although the period of delirium was difficult to determine accurately, the estimated duration previous to the first examination ranged from six days to three to six weeks, except in the case of J. S. (case 17), who had been known to be confused intermittently for perhaps one year. This patient had a stage V electroencephalogram. The clinical condition of L. S. (case 14) became worse between his first and his second examination, this change being reflected in the electroencephalogram (fig. 5). Three patients showed

degree of change in the electroencephalogram disparate with his psychologic status. One of the most interesting evidences of the primary disturbance in carbohydrate metabolism in this patient was the hypoglycemic reactions, with confusion and increasingly abnormal electroencephalographic changes, which occurred at levels of the blood sugar not usually associated in normal persons with such pronounced clinical signs and symptoms of hypoglycemia. This phenomenon, which has been pointed out previously,[10] suggests the possibility of a lowered threshold of
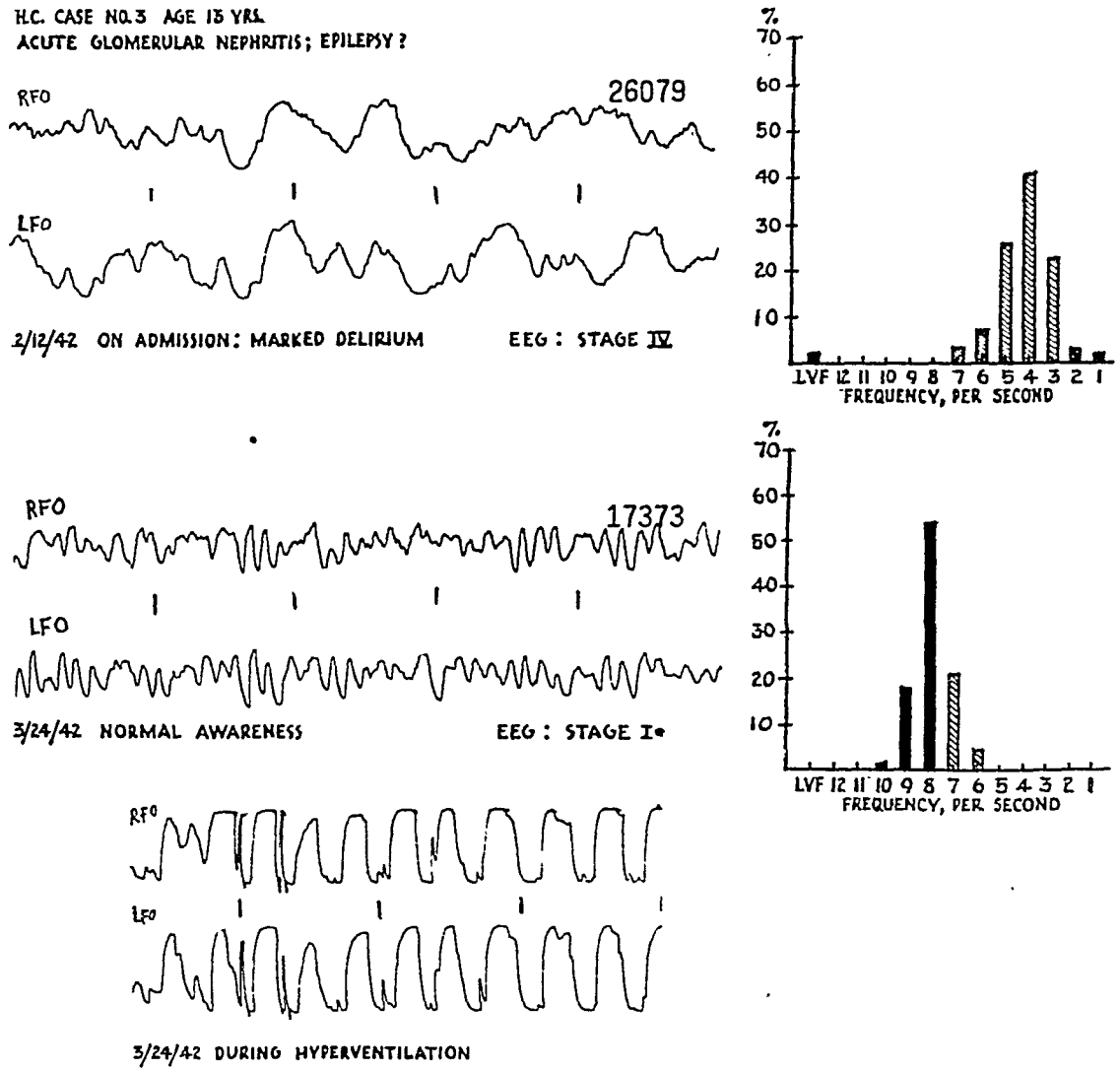
Fig. 3.—Delirium in a case of probable epilepsy with acute glomerulonephritis.
After the delirium had completely cleared, the electroencephalogram still showed runs of high voltage slow waves among normal frequencies, and on hyperventilation a wave and spike pattern appeared.

stage II electroencephalograms and were considered to be moderately confused. The remaining 2 patients with stage II electroencephalograms had Addison's disease. The electroencephalograms of patients with Addison's disease have been shown to be abnormal[6] even when replacement t h e r a p y is presumably adequate and the patient has returned to normal social activity. One of the 2 patients with this disease (R. W., case 22) presented a

reaction in patients with Addison's disease. Both patients with this condition were in mild crisis at

10. Thorn, G. W.; Koepf, G. F.; Lewis, R. A., and Olsen, E. F.: Carbohydrate Metabolism in Addison's Disease, J. Clin. Investigation **19**:813, 1940. Engel, G. L., and Margolin, S. G.: Neuropsychiatric Disturbances in Addison's Disease and the Role of Impaired Carbohydrate Metabolism in the Production of Abnormal Cerebral Function, Arch. Neurol. & Psychiat. **45**:881 (May) 1941.

CASE 19.—G. A., a man aged 60. Chronic bronchitis and asthma; emphysema; failure of right side of heart; polycythemia. Duration of delirium before first examination, two to three weeks. Admission, Dec. 1, 1941.

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
12/3	Moderate	III	Oxygen saturation of arterial blood 79%; carbon dioxide content 59.2 volumes %; red blood cells 6,290,000 per cu. mm.; venous pressure 210 mm. of water; circulation time 20 sec.; vital capacity 1,500 cc.
12/16	Mild	III-II	Oxygen saturation of arterial blood 87.3%; carbon dioxide content 54.05 volumes %; venous pressure 75 mm. of water; circulation time 19 sec.; vital capacity 1,800 cc.
12/19	Mild	II-I	Oxygen saturation of arterial blood 88.5%; carbon dioxide content 55.5 volumes %

CASE 20.—D. Mc., a girl aged 13 years. Chorea minor; acute rheumatic heart disease; congestive heart failure. Duration of delirium before first examination, six days. Admission, Jan. 10, 1942.

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
1/12	Severe	IV	Severe chorea; mutism; temperature 103 F.; moderate left ventricular failure
1/22	Moderate	IV-III	Temperature normal for 3 days; decreased pulmonary congestion
2/14	Mild	II-I	Patient afebrile and free from chorea for 2 weeks
2/19	Mild	II-I	No change in patient's condition

CASE 21.—E. M., a woman aged 62. Addison's disease; pulmonary tuberculosis. Duration of delirium before first examination, six weeks. Admission, March 18, 1942.

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
3/20	Moderate	II	Urea nitrogen 21 mg per 100 cc.; sodium 120 mEq./L.; chloride 89 mEq./L.; blood pressure 105/70; weight 45.6 Kg.; hematocrit reading 48%
3/27	Mild	Normal	3/20-3/27: 20 mg. of desoxycorticosterone acetate and 95 cc. of adrenal cortex extract (Upjohn) injected intramuscularly (20 cc. of extract 3/27); 15 Gm. of sodium chloride daily; sodium 134 mEq./L.; chloride 104 mEq./L.; temperature 101 F.
4/7	Mild to moderate	I-II	3/28-4/7: 2 mg. of desoxycorticosterone acetate injected intramuscularly daily; 5-11 Gm. of sodium chloride daily weight 50 Kg.; blood pressure 124/70 to 170/100; hematocrit reading 28%; sodium 140 mEq./L.; chlorides 111 mEq./L.; temperature 99 to 101 F.; roentgenogram of the chest showed increase of exudative lesions
4/13	Mild	I	4/8-4/11: 10 cc. adrenal cortex extract daily; 4/12: 20 cc. of extract; 4/13: 38 cc. of extract and 9 Gm. sodium chloride daily; weight 47.8 Kg.; blood pressure 140/90 to 150/110; hematocrit reading 28%

CASE 22.—R. W., a man aged 59. Addison's disease. Duration of delirium before first examination unknown. First admission, Oct. 6, 1941.

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
10/10/41	Mild	II	Mild crisis. Blood pressure 102/70; sodium 130 mEq./L.; hematocrit reading 47%; no medication; weight 76.8 Kg.
10/15	Mild	II	Crisis more severe. Blood pressure 85/50; sodium 130 mEq./L.; 1 injection of 10 mg. desoxycorticosterone acetate and 1 injection of 5 cc. adrenal cortex extract; 60 Gm. sodium chloride in 3 days
10/22	Mild	II	Medication: 3 mg. desoxycorticosterone acetate daily; 9 Gm. of sodium chloride daily. Hematocrit reading 46%; sodium 135 mEq./L.
11/7	Mild	II-I	Medication: 1 mg. desoxycorticosterone acetate daily; 4 Gm. of sodium chloride daily. Hematocrit reading 39%; sodium 140 mEq./L.; blood pressure 125/90; weight 74.6 Kg.
11/12	None	I	Medication same as that for 11/7. Hematocrit reading 40%; blood pressure 125/73. Patient discharged from hospital
12/15	None	I	Good clinical condition: blood pressure 100/85. Medication: 1 mg. desoxycorticosterone acetate daily; 5 Gm. sodium chloride daily; 60 mg. thiamine hydrochloride daily *
1/3/42	None	I	Clinical condition good. Medication: 1 mg. desoxycorticosterone acetate daily; 6 Gm. of sodium chloride daily; 300 mg. nicotinamide daily. Blood pressure 120/80
2/20	None	I	Clinical condition good. Medication: desoxycorticosterone acetate and sodium chloride same as that of 1/3; 25 mg. calcium pantothenate daily. Weight 81.2 Kg.; blood pressure 125/75; hematocrit reading 44%
3/31	None	I	Clinical condition good. Medication: desoxycorticosterone acetate and sodium chloride same as before; 12 mg. riboflavin daily. Weight 82 Kg.; sodium 137 mEq./L.; chloride 110 mEq./L.
4/4	None	I to normal pattern	Clinical condition good. Medication: 15 cc. adrenal cortex extract daily for 4 days; 47.5 cc. of extract on 4/4
4/14	Mild	II	Mild crisis; acute pyelitis; temperature 102 F. Medication (4/8 to 4/14): desoxycorticosterone acetate 3 to 7 mg. daily; adrenal cortex extract 10 to 20 cc. daily; dextrose in saline solution, 4 to 6,000 cc.; 1 Gm. sulfadiazine daily. Hematocrit reading 47 to 36%; sodium 127 mEq./L.; blood pressure 110/70 to 125/80

* Merck & Company, Inc., Rahway, N. J., furnished the vitamins used in this experiment.

Of this group of 10 patients, the electroencephalograms of 5 showed evidence of stage IV or stage V. This most prominent electroencephalographic abnormality correlated in each

After administration of 107 cc. of adrenal cortex extract (Upjohn) [11] in five days, the electroencephalogram became nearly normal, and no hypoglycemic reaction developed during the dextrose tolerance test. E. M. (case 21) also showed corresponding clinical and electroencephalographic improvement with 95 cc. of adrenal cor-

and R. W., case 22, with acute pyelitis) prevented repetition of these experiments.

A more detailed report on the electroencephalogram and the cerebral metabolism in Addison's disease will appear later.[12]

The following case is illustrative of group 2 (fig. 5):
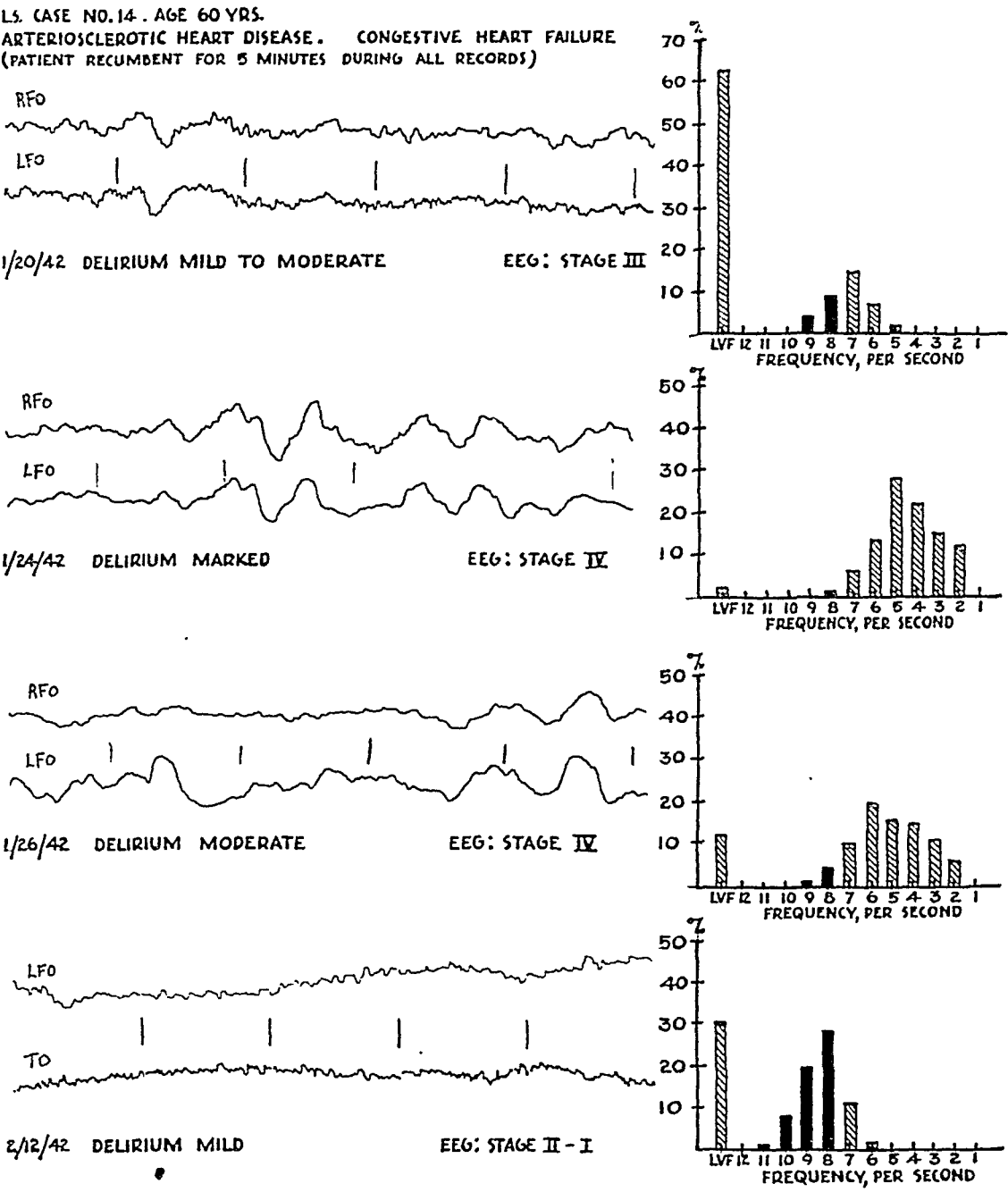
Fig. 5.—Partial recovery from delirium in a case of congestive heart failure due to arteriosclerotic heart disease.

Clinically the patient became worse before he became better, and this is also apparent in the electroencephalogram.

tex extract, administered in six days. The electroencephalogram in this case became entirely normal. The presence of infection (E. M., case 21, with exacerbation of pulmonary tuberculosis,

History.—L. S. (case 14), a Negro aged 66, was admitted to the Peter Bent Brigham Hospital on Jan. 19, 1942 because of increasing dyspnea.

11. The Upjohn Company, Kalamazoo, Mich., supplied the adrenal cortex extract.

12. Romano, J., and Engel, G. L.: The Significance of the Electroencephalographic Changes in Addison's Disease. to be published.

the time of initial examination and showed mild to moderate confusion. R. W. responded well clinically to desoxycorticosterone acetate:

dences of disturbed awareness could be elicited. Repeated examinations over the course of five months of treatment with desoxycorticosterone
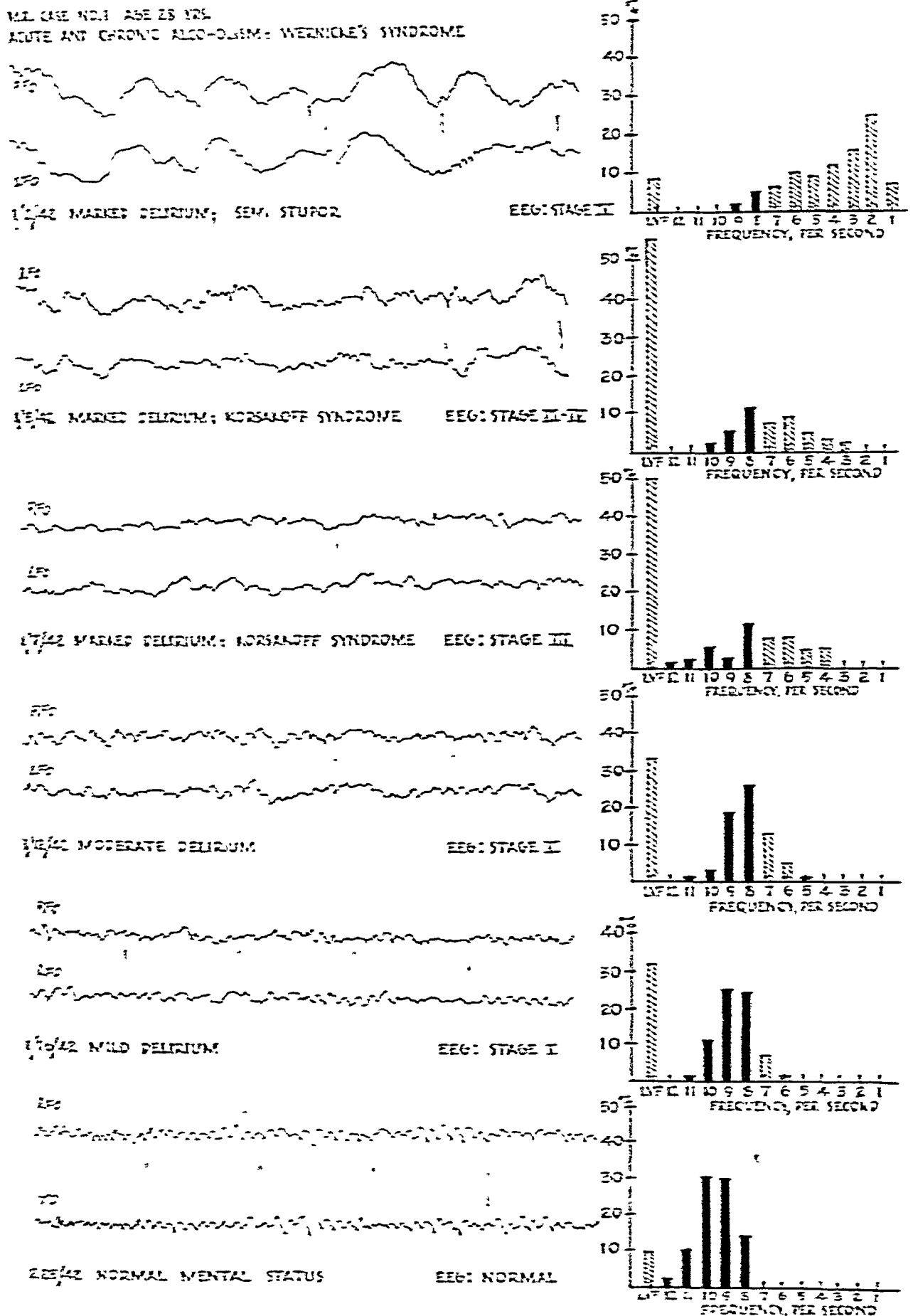
Fig. 4—Complete recovery in a case of acute and chronic alcoholism with Wernicke's encephalopathy. The electroencephalogram passed through all phases from stage IV to normal with corresponding improvement in the mental status.

Although the electroencephalographic pattern improved, it remained abnormal when no evi-

acetate and various supplemental vitamins of the B complex group revealed no essential change

CASE 26.—*W. F., a man aged 46. Malignant hypertension; uremia.* Duration of delirium before first examination, two to three weeks. Admission, Jan. 15, 1942.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
1/19	Severe	IV (fig. 6)	Blood pressure 240/105; cerebrospinal fluid pressure 410 mm. of water; nonprotein nitrogen 73 mg. per 100 cc.; venous pressure elevated; pulmonary congestion; Chene-Stokes respiration; hemoglobin 11.7 Gm. per 100 cc.
2/16	Mild	V	Numerous convulsive seizures and great confusion in first 3 wk. 2/6/42; considerable improvement; blood pressure 250/120; increase in urea nitrogen content of blood from 80 to 119 and 160 mg. per 100 cc.; carbon dioxide content 48 volumes %; chlorides 98 mEq./L.; hemoglobin 8 Gm. per 100 cc.

* The patient died in the hospital in the latter part of February 1942. Autopsy was performed.

CASE 27.—*J. M., a man aged 74. Chronic alcoholism; cirrhosis of liver; pneumonia; acute empyema; congestive heart failure. Duration of delirium before first examination unknown. Admission, Dec. 11, 1941.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
12/24/41	Severe	IV	Icteric index 54; venous pressure 205 mm. of water; hemoglobin 10.9 Gm./100 cc. Pneumonic process subsiding; early evidence of empyema. Temperature 101 F.; oxygen saturation of arterial blood 94.2%
12/30	Less severe	IV-V	Icteric index 40; temperature 99-100 F.
1/16/42	Unchanged	IV-V	Icteric index 18; temperature 100.5 F.; venous pressure 100 mm. of water, with increase on compression of liver to 200 mm. of water; oxygen saturation of arterial blood 94.7%
1/21	Unchanged	V	Empyema
4/30	Unchanged	V	Area of empyema drained surgically 1/26/42. Clinical improvement; no icterus or congestive heart failure. Wound well healed. Patient followed in outpatient department

CASE 28.—*S. J., a man aged 60. Tuberculous pericarditis; exfoliating erythrodermatitis; emaciation.* Duration of delirium before first examination, two weeks (?). Admission, Dec. 8, 1941.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
12/18	Mild	I	Hydrothorax and ascites; venous pressure 55 mm. of water; circulation time 15 sec.; vital capacity 1,300 cc.; fever
1/9	Not tested	II	Severe ulcerative stomatitis, exfoliative dermatitis and generalized edema. Patient appeared drowsy but could not be tested formally because of oral lesions

* The patient died in the hospital on Jan. 18, 1942. Autopsy was performed.

CASE 29.—*S. H., a man aged 63. Addison's disease.* Duration of delirium before first examination, six weeks (?). Admission, Feb. 9, 1942.*

| Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
2/13	Moderate	III (?)	Mild crisis. Blood pressure 92/68; hematocrit reading 41%; urea nitrogen content of blood 30 mg./100 cc.; sodium 136 mEq./L.; chlorides 102 mEq./L. Medication: 6 Gm. sodium chloride daily. Weight 43 Kg.
3/9	Moderate; slight improvement	III to II (?)	Blood pressure 100/60; weight 47.2 Kg.; sodium 131 mEq./L.; hematocrit reading 35%. Medication: 15 Gm. sodium chloride daily; 4 cc. of adrenal cortex extract (of doubtful potency) daily for 4 days
5/8	Unchanged	III to II (?)	Patient discharged from hospital 3/9. Since 4/7 daily administration of 1 mg. desoxycorticosterone acetate and 15 Gm. sodium chloride. 4/13: sodium 119 mEq./L. 5/8: poor appetite, weakness and fatigue; blood pressure 105/75; sodium 147 mEq./L.; chlorides 112 mEq./L.

* The therapy of this patient was not under our direct supervision.

CASE 30.—*A. S., a woman aged 59. Pernicious anemia; combined system disease. Duration of delirium before first examination, six weeks (?). Admission, Feb. 26, 1942.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
3/6	Moderate	III (?)	Hemoglobin 7.6 Gm./100 cc.; red cells 2,000,000 per cu. mm.; reticulocyte count 18%. Since 2/27 daily intramuscular injections of 1 cc. liver extract
3/24	Moderate	III (?)	Hemoglobin 9.7 Gm./100 cc.; red cells 3,110,000 per cu. mm.
5/9	Slight improvement	III (?)	Liver therapy stated to be adequate; patient followed in outpatient department

The 8 patients in this group were all chronically ill. For a number it was not possible to establish the total duration of the delirium, but several apparently had had disturbances in awareness for as long as a year. The factors responsible for the prolongation of the delirious state varied. Three patients (cases 23, 27 and 30) undoubtedly had long-standing vascular and degenerative changes associated with age which greatly decreased the essential reversibility of the reaction to the underlying physical disease. The other patients suffered from diseases which ran a chronic, and often progressive, course. The patient with Addison's disease had not received adequate replacement therapy on any of the three occasions on which she was studied.

Three patients (cases 25, 26 and 28) in this group eventually died. Two of these patients (cases 25 and 28) presented postmortem evidence of cerebral edema. In the other patient (case 26), with dermatomyositis, numerous infil-

The patient had first manifested exertional dyspnea and paroxysmal nocturnal dyspnea two years before. On admission to the hospital at that time he had peripheral edema, pulmonary congestion, an enlarged heart and hypertension (155 systolic and 115 diastolic), and the electrocardiogram showed a prolonged PR interval and intraventricular block. He improved rapidly under a regimen of rest and administration of digitalis and diuretics. After discharge he was observed in the outpatient department.

Five weeks before admission increasing dyspnea, attacks of paroxysmal nocturnal dyspnea, edema of the ankles and swelling of the abdomen developed, and he gained 14 pounds (6.4 Kg.) in weight in two and a half weeks.

Examination.—Physical examination revealed dyspnea and orthopnea. The veins of the neck were distended and filled further on compression of the liver. The heart was enlarged to the left anterior axillary line, where a prominent apical impulse was noted in the sixth interspace. The blood pressure was 105 systolic and 85 diastolic. There were dulness and diminished breath sounds at the base of the right lung, and moist rales were heard in both lungs up to the angle of the scapula. There was ascites, and the edge of the liver was felt 3 fingerbreadths below the costal margin. There was pronounced pitting edema over the sacrum and legs.

Course of Illness.—First Examination (January 20): The patient was jocular and somewhat euphoric. He was correctly oriented. Memory and recall were defective. Attention was fair, and he carried out serial subtraction tests methodically, but with several errors. He interpreted proverbs well. There was no confabulation, either spontaneous or provoked.

Electroencephalogram (fig. 5): With the patient lying almost flat, the test was begun immediately; the record was predominantly one of low voltage fast activity, with 24 per cent 5 to 7 per second activity and 13 per cent 8 to 9 per second activity (stage III).

Physiologic data are listed in the accompanying tabulation (case 14).

Second Examination (January 24): There had been moderate diuresis, with decrease in edema, but the patient was still dyspneic and othopneic and experienced frequent episodes of paroxysmal nocturnal dyspnea. He was now noted to be confused at night, mistook his room for "a small room in the First National Bank," "a movie theater" or "Massachusetts Avenue" and experienced disturbing dreams. Examination revealed little change in the degree of congestive heart failure. When the patient was tested in the laboratory, he appeared confused and bewildered. He expressed the feeling that he was now living in "Biblical times" and that each minute represented "a thousand years." He spoke about the Bible and religion, intermingling these comments with more prosaic conversation. He was somewhat irritable. Attention fluctuated considerably, and he was unable to carry out serial subtractions. Memory was poor, and he had difficulty in interpreting proverbs.

The electroencephalogram was irregular and slow, with many large slow waves (stage IV).

Third Examination (January 26): Signs of congestive heart failure had diminished somewhat. The patient was more quiet and less irritable. He was still confused and referred frequently to religious matters. He was correctly oriented, but attention fluctuated and memory was only fair. He was now able to do serial subtractions, but with numerous errors and frequent

loss of place. He had difficulty in interpreting proverbs, and confabulation could be provoked.

Electroencephalogram: At the onset of the examination and with the patient recumbent, the electroencephalogram showed predominantly slow activity, which was somewhat less irregular than on the previous occasion. The pattern was still that of stage IV.

Fourth Examination (February 12): The patient had now largely recovered from the heart failure and was ready for discharge. He had not been confused at night for more than ten days. He was correctly oriented and more attentive. Memory was still defective, and serial subtraction was done with a number of errors, although with better sustained attention. Some confabulation could still be provoked.

The electroencephalogram now showed a beginning regular pattern, with 58 per cent normal frequencies, 13 per cent 6 to 7 per second activity and 31 per cent fast activity. The record represented a phase between stage II and stage I.

Group 3.—Eight patients showed little or no change in the level of awareness or became worse during the period of observation.

CASE 23.—*G. S., a woman aged 71. Hypertension and arteriosclerotic heart disease; congestive heart failure. Duration of delirium before first examination, one year. Admission, Sept. 22, 1941.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
9/24	Severe	V	Moderately severe congestive heart failure
9/26	Severe	V	Less severe congestive heart failure
10/9	Severe	V	No congestive failure: slight shift toward faster and more normal frequencies in electroencephalogram

CASE 24.—*S. F., a woman aged 54. Rheumatic valvular disease; chronic congestive heart failure. Duration of delirium before first examination, one year. Admission, Sept. 26, 1941.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
9/29	Severe	V	Severe congestive heart failure
1/6	Severe	V	Severe congestive heart failure

CASE 25.—*O. K., a woman aged 23. Libman-Sacks syndrome with dermatomyositis; severe emaciation.* Duration of delirium before first examination unknown. Admission, Feb. 12, 1942.

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
3/14	Moderate	IV-V	Five year history of intermittent involvement of joints, skin, lungs and muscles, with extreme emaciation; onset of present episode 3 months before admission. Weight 32.7 Kg.; temperature 102 F.
3/26	Moderate to severe	V	Weight 25.4 Kg.; extreme exhaustion and asthenia
4/23	Moderate	V	Some clinical improvement; weight 30 Kg.; temperature 101 F.

* The patient was discharged on May 1, 1942 to return home; she lapsed into coma and died May 3. An autopsy was performed.

Group 4.—Three patients presented electro-encephalographic changes indicative of focal and diffuse cerebral involvement.

CASE 31.—*H. B., a man aged 55. Presenile cerebral atrophy; epilepsy. Duration of delirium before first examination unknown. Admission, Nov. 18, 1941.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
11/21/41	Mild	Frontal, III-IV; occipital, I	Recurrent spells of confusion and convulsions for preceding 5 yr. Clinical studies, including pneumoencephalographic tests, indicated presenile atrophy of frontal lobes. Patient had had generalized convulsion the morning of November 21
11/24	Mild	Frontal, IV, occipital, II	Seizure on 11/22
11/28	Moderate	Frontal, IV, occipital, II	No seizure since 11/22
12/4	Mild	Frontal, II, occipital, I	Pneumoencephalogram on 12/1
12/29	Mild	Frontal, II, occipital, I	Seizure on 12/28
1/9/42	None	Frontal, II-III; occipital, I-II	Seizure a few days before
3/30	None	Frontal, I; occipital, I	With diphenylhydantoin therapy. 0.1 Gm. three times daily; no seizures

CASE 32.—*R. G., a woman aged 54. Presenile cerebral atrophy (?); diabetes mellitus, controlled; hypertensive cardiovascular disease, compensated. Duration of delirium before first examination unknown. Admission, April 25, 1942.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
4/29	Severe	Frontal, IV; occipital, I-II	Diabetes controlled; questionable past history of cerebral vascular accident: blood pressure 190/110; pressure and dynamics of cerebrospinal fluid normal; protein 55 mg./100 cc.; lymphocytes 2 per cu. mm.; urea nitrogen of blood 13 mg./100 cc.; blood sugar 92 mg./100 cc.
5/8	Severe	Frontal, IV; occipital, I-II	No essential change in clinical or laboratory data

CASE 33.—*I. A., a woman aged 55. Meningitis (Pneumococcus type 17); thrombosis of leptomeningeal vessels; encephalomalacia.* Duration of delirium before first examination, one month. Admission, February 1942.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
2/14/42	Severe	Left frontal region IV; occipital, II	Patient had received specific antipneumococcic serum and sulfadiazine; remained stuporous

* Patient died in the middle of March 1942. An autopsy was performed.

Each of the patients in this group had focal electrical disturbances which originated in the frontal areas and spread diffusely to a varying degree.

Although we used the previously noted classification of electroencephalographic stages for the records of this group, they presented certain noteworthy differences from those of the previous group. All these patients had foci in the frontal areas in which the electroencephalographic changes were comparable to the previously established gradations. Tracings taken simultaneously from the frontal, temporal, parietal and occipital areas revealed that the high potential slow waves originating in the frontal areas spread posteriorly, with a slight time lag and in a progressively diminishing proportion. The occipital region thus presented an essentially normal pattern interrupted by groups of high potential slow waves, which coincided with the appearance of waves of higher potential and slower frequency in the frontal area. Two of the patients (R. G., case 32, and I. A., case 33) were studied incompletely. I. A. died, and autopsy established evidence of encephalomalacia involving the frontal lobes. The further course of R. G.'s illness is unknown.

The case of H. B. (case 31) presented certain features worthy of comment. The patient, a man aged 55, had experienced spells of confusion for at least five years, and more recently had had convulsive seizures. Although his seizures had clonic phases, they were characterized principally by peculiar slow, repetitive, stereotyped movements of the face and the extremities. Confusion was evident at times before such seizures and usually occurred afterward. Occasionally the patient experienced peculiar aphasic-like confused periods without any disturbances in movement. His interim status was that of early dementia. Pneumoencephalographic study revealed considerable dilation of the ventricular and subarachnoid spaces. The left ventricle was more dilated anteriorly and was displaced slightly to the left, having apparently been drawn there by shrinkage of the left anterior frontal area. There was increased air about the island of Reil on both sides.

The patient was studied for five months, during which time he had occasional seizures and periods of confusion. Prominent electroencephalographic changes in the frontal areas were always noted during periods of confusion. However, on one occasion (January 9), two days after a seizure, there were moderate electroencephalographic changes in the frontal area although his awareness was good. After diphenylhydantoin therapy (one month), with no seizures, the electroencephalographic changes were minimal and his awareness was intact. These data, together with those obtained for H. C. (acute glomerulonephritis and epilepsy), group 1, case 3, lead us to believe that certain components of the electrical disturbances in epileptic patients are not directly correlated with changes in the level of awareness.

The electroencephalographic changes for H. B. are illustrated in figure 7.

Group 5.—This group of 11 patients consisted of persons who died before more than one examination could be carried out.

trative lesions of small vessels leading to small, granuloma-like foci of gliosis were noted in the brain. The question of morphologic alterations in the brain will be discussed in a subsequent section.

Correlation of the electroencephalogram with the mental status was again good. Five patients were greatly confused, and all had stage IV to stage V electroencephalograms. The 2 patients with stage III electroencephalograms showed moderate confusion, while S. J. (case 28), with a stage I electroencephalogram, was only mildly

We hope to be able to settle this point by observing other patients with records of this type who improve clinically.

W. F. (case 28) demonstrated the transition of the electroencephalographic pattern from stage IV to stage V (fig. 6). This patient, a man aged 46, entered the hospital with malignant hypertension and hypertensive encephalopathy. At the time of admission the blood pressure was 240 systolic and 165 diastolic; there was evidence of left and right ventricular failure, and the cerebrospinal fluid pressure was elevated to 410 mm. of water. The nonprotein nitrogen content of the blood was 73 mg. per hundred
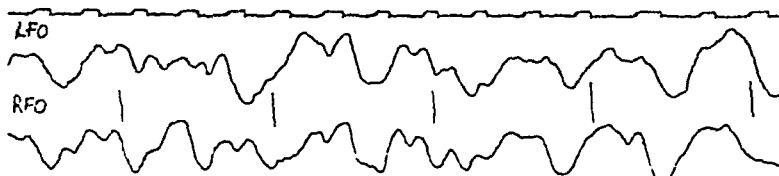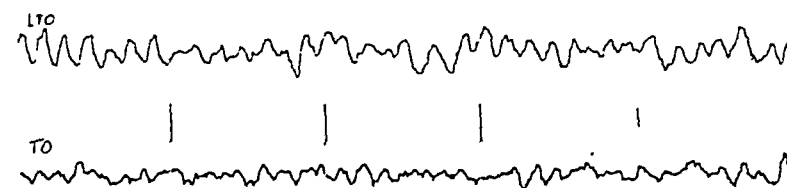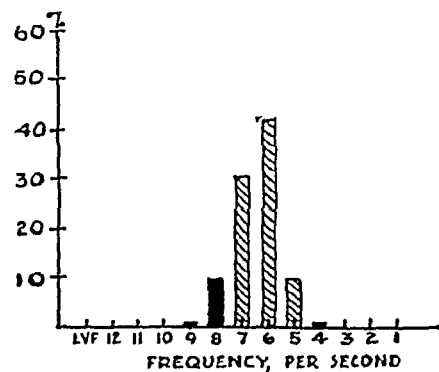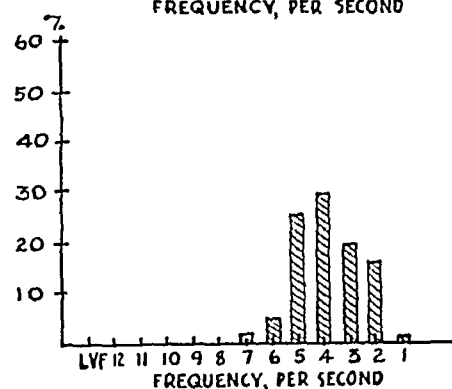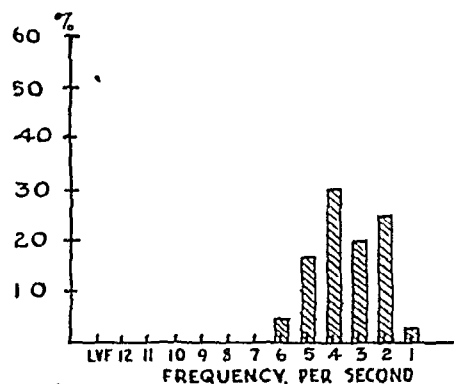
Fig. 6.—Progression from stage IV to stage V in a case of prolonged delirium due to malignant hypertension and uremia. A phasic difference during Cheyne-Stokes respiration is also illustrated. In this patient the mental status improved considerably during the transition from stage IV to V.

confused. There was some uncertainty in the interpretation of the electroencephalograms of A. S. (case 30) and S. H. (case 29). Both these records consisted chiefly of irregular, low voltage fast activity with small amounts of irregular, slow activity. Both the patients showed moderate disturbances in the level of awareness, but as neither the clinical state nor the electroencephalogram changed significantly during the period of observation, we cannot state with finality that this electroencephalographic pattern represented stage III, and not a normal low alpha record.

cubic centimeters. The patient was extremely confused; his attention fluctuated greatly during Cheyne-Stokes respiration, and the electroencephalogram was totally disorganized, irregular and slow. He remained in this state for three weeks, during which period a number of convulsions occurred. When the patient was reexamined about one month later, the degree of confusion had lessened considerably; convulsions had ceased, but there were increasing retention of urea nitrogen and anemia. The electroencephalogram at this stage showed a great increase in regularity but was still predominantly slow, and there was no change when the patient opened his eyes. Several days after this the patient lapsed into coma and died.

These changes are illustrated in figure 6.

CASE 34.—*M. B., a woman aged 68. Myocardial infarction; acute congestive heart failure. Duration of delirium before first examination, two weeks. Admission, Feb. 10, 1942.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
2/18	Severe	IV	Venous pressure 190 mm. of water; circulation time 26 sec.; Cheyne-Stokes respiration. Patient died Feb. 20, 1942

CASE 35.—*E. C., a woman aged 53. Chronic rheumatic heart disease; mitral stenosis and insufficiency; congestive heart failure; thrombosis of superior vena cava and left internal jugular and left subclavian veins. Duration of delirium before first examination, three weeks. Admission, Nov. 3, 1941.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
11/19/41	Severe	IV	Venous pressure, right arm, 150 mm. water, with rise to 180 mm. of water with compression of liver; circulation time 28 sec.; oxygen saturation of arterial blood 91.2%; carbon dioxide content of arterial blood, 38.04 volumes %. Patient died

CASE 36.—*R. B., a woman aged 73. Hypertensive heart disease; complete heart block; congestive heart failure. Duration of delirium before first examination, ten days. Admission, March 21, 1942.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
3/24/42	Severe; semistupor	IV	Venous pressure 205 mm. of water; circulation time (dehydrocholic acid) 45 sec., (potassium ferrocyanide) 46 sec.; complete heart block; heart rate 24. Death 3/25

CASE 37.—*F. A., a man aged 67. Chronic bronchitis; asthma; emphysema; pulmonary fibrosis; right and left ventricular failure. Duration of delirium before first examination, two weeks. Admission, Feb. 17, 1942.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
2/19/42	Severe	II-III	Venous pressure 140 mm. water, increased on compression of liver to 180 mm. water; circulation time 35 sec.; vital capacity 1,500 cc.; oxygen saturation of arterial blood 69%; carbon dioxide content of arterial blood 65.3 volumes %; red cells 6,100,000 per cu. mm. Patient died 2/22/42

CASE 38.—*M. P., a woman aged 43. Chronic alcoholism; cirrhosis of liver; hypercholemia; anemia. Duration of delirium before first examination, two to three weeks. Admission, Jan. 15, 1942.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
1/19	Severe	IV	Deep jaundice; icteric index 80; temperature 101 F.; red blood cells 1,800,000; hemoglobin 7 Gm./100 cc. Patient died January 1942

CASE 39.—*F. G., a man aged 84. Obstructive jaundice; acute left ventricular failure. Duration of delirium before first examination, two weeks. Admission, Jan. 2, 1942.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
1/9/42	Severe	IV	Intense jaundice; icteric index 108; Cheyne-Stokes respiration; congestive heart failure present on admission, but not at time of examination. Patient discharged to home for incurables and died shortly thereafter

CASE 40.—*E. D., a woman aged 60. Congenital polycystic kidneys; uremia. Duration of delirium before first examination, one to two weeks. Admission, Nov. 28, 1941.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
12/3/41	Severe	IV-V	Early signs of impending uremia for 6 mo.; Kussmaul breathing for 5-6 days; nonprotein nitrogen 286 mg./100 cc. carbon dioxide content of arterial blood 23.6 vols.%; hemoglobin 7.5 Gm./100 cc.; blood pressure 180/110. Patient died

CASE 41.—*D. B., a man aged 33. Malignant hypertension; uremia. Duration of delirium before first examination, four weeks. Admission, Nov. 23, 1941.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
11/27	Severe; stupor	IV	Hypertension for 3 yr.; headache and vomiting 4 wk.; six convulsions on 11/24/41; blood pressure 230/160; cerebrospinal fluid pressure 600 mm. of water; fluid xanthochromic; total protein content 120 mg./100 cc. Urine: specific gravity 1.009; albumin 4+; many red cells; urea nitrogen of blood 61 mg./100 cc. Patient died 11/30

CASE 42.—*J. N., a man aged 76. Pneumonia, lower lobe of right lung; empyema; bacteremia (Pneumococcus type IV); chronic alcoholism. Duration of delirium before first examination unknown. Admission, March 20, 1942.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
3/23	Severe	IV	Temperature 102 F.; oxygen saturation of arterial blood 95.6/100 cc. Patient died

CASE 43.—*O. M., a man aged 72. Myocardial infarction; hemiplegia of embolic origin. (?) Duration of delirium before first examination, two to three weeks. Admission, Feb. 1, 1942.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
2/24	Severe	IV	Cheyne-Stokes respiration; oxygen saturation of arterial blood, apneic phase, 91.7%; dyspneic phase, 94.5%. Patient died
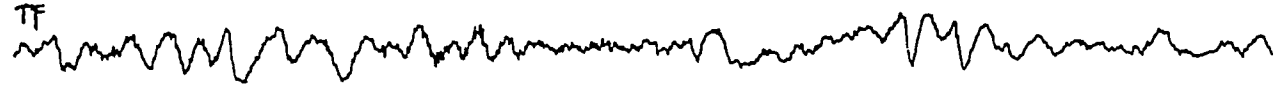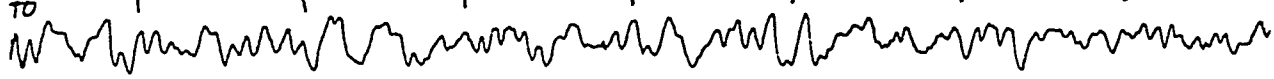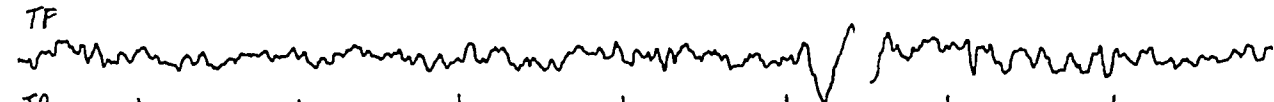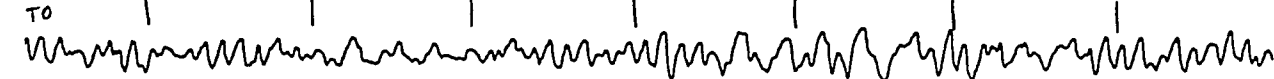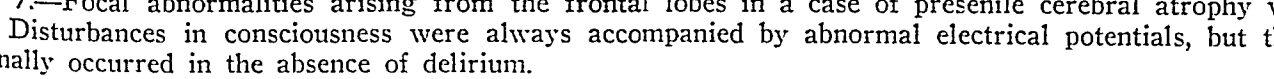
Fig. 7.—Focal abnormalities arising from the frontal lobes in a case of presenile cerebral atrophy with epilepsy. Disturbances in consciousness were always accompanied by abnormal electrical potentials, but the latter occasionally occurred in the absence of delirium.

CASE 53.—*J. T., a man aged 38. Chronic alcoholism (?); head trauma. Duration of delirium before first examination unknown. Admission, Oct. 13, 1941.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
10/14	Severe	III	Comatose state on admission, but patient more aware, active and delirious during examination

The correlation between age and course of illness for the 53 patients may be noted. Fifteen patients were between the ages of 13 and 50; 11 patients, between 50 and 60; 17 patients, between 60 and 70, and 10 patients were more than 70. Forty-one patients were studied long enough for the eventual outcome to be established. Of the 12 patients who recovered completely, or nearly completely, 7 were less than 50 years of age. In contrast, of the 29 patients who recovered partially (group 2), who failed to improve (group 3) or who died (group 5), only 7 were less than 50 years of age.

COMMENT

The data presented demonstrate that delirium as defined in this paper is associated with an electrical disturbance of the brain which may be reversible to the extent that the delirium is reversible. Additional data, which will be discussed in more detail in an accompanying report,[13] have also indicated that the electrical abnormality may be favorably influenced more specifically by supply of missing metabolic elements, such as oxygen, dextrose, blood or adrenal cortex extract.

The electrical abnormalities observed are consistent with changes to be expected when the basic integrity of the nerve cell and its environment are disturbed. These abnormalities include, in order of intensity: (1) decrease in frequency, (2) disorganization and (3) reorganization at a lower energy level. Decrease in frequency implies decreasing levels of or decreasing responses to cortical excitation, which, in turn, may be due to a decrease in the metabolic activities of the neurons or to a decrease in the effect of afferent impulses to the cortex, such as occurs normally in sleep. Disorganization implies a disturbance in the synchronizing or pace-making mechanisms and would be expected to represent a more pronounced response to a noxious factor acting diffusely. With the continuation of the process the pattern tends to reorganize at a slower frequency with higher amplitude, i. e., at a lower energy level. Thus, stages I and II might represent the first phase; stages III and IV, the phase of disorganization, and stage V, the phase of reorganization at a lower energy level. The diminished effect of afferent impulses on the electrical pattern in the late phases is demonstrated by the lack of effect on stages III, IV and V of opening

and closing the eyes. Any of these stages were reversible. In certain instances in which the electroencephalogram had returned to normal, the psychologic status of the patient revealed some degree of intellectual deficit. This minimal dementia is possibly due to the complete destruction of certain nerve cells while the essential electrical pattern of the remaining cells returns to normal. Recent observations have revealed a number of patients with long-standing dementia of gradual development and with cortical atrophy, demonstrated pneumoencephalographically, whose electroencephalograms were entirely normal.[14] These data support the view that the abnormal electrical activity arises from damaged or dying cells. The intensity and reversibility of the electrical disturbance were directly correlated with the speed of onset, the intensity and duration of the noxious stimulus and the basic premorbid integrity of the central nervous system, particularly as it was influenced by factors of age, nutritive state and circulatory efficiency.

It is noteworthy that these electroencephalographic changes are essentially the same as those which have previously been reported in association with acute and chronic cerebral trauma,[15] encephalitis,[5a] neurosyphilis,[5f] increased intracranial pressure,[5e] hypoglycemia,[4d] the administration of certain drugs which influence consciousness[4e] and certain focal cerebral lesions which are reversible. Further, we have observed essentially the same electroencephalographic stages in a condensed form during syncope and as a result of a variety of causes.[16] These data obtained by independent observers offer further evidence of the nonspecificity of these electroencephalographic changes.

The relation of these electroencephalographic changes to epilepsy is not clear to us. Five of our patients had convulsions more than once. Three patients had convulsions antedating the delirious episodes (H. B., case 31; E. M., case 9, and H. C., case 3). For at least 1 of these 3 patients (H. C., case 3) the interseizure record was unmistakably diagnostic of epilepsy (wave and spike pattern) at a time when no disturbance in behavior was demonstrable, while the delirious episodes of the other 2 patients were directly associated with the seizures. The fourth and fifth patients (W. F., case 26, and D. B., case 41) both had repeated seizures during late stages of malignant hypertension but had no past or family history of epilepsy. During the epi-

14. Engel, G. L.: Unpublished data.

15. Jasper and others.[5b] Williams, footnote 5 c and 5 d.

16. Engel, G. L.; Romano, J., and McLin, T.: Vasodepressor and Carotid Sinus Syncope: Clinical, Electroencephalographic and Electrocardiographic Observations, Arch. Int. Med., to be published.

CASE 44.—*J. C., a woman aged 46. Previous bilateral mastectomy; carcinoma of breast, with metastases to skin, lymph nodes, lung, pleura and brain (?); severe emaciation. Duration of delirium before first examination, two months. Admission, Oct. 28, 1941.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
10/29	Moderate	II	Formed visual hallucinations; dyspnea; vital capacity 1,000 cc. Patient died 10/31/41

All but 1 of the patients in group 5 had pronounced disturbances in the level of awareness. The exception (J. C., case 44) became stuporous shortly after the examination. Nine of the 11 patients showed stage IV electroencephalograms, and the remaining 2 patients, stage III and stage II electroencephalograms respectively. Although all these patients died shortly after examination, the 4 patients for whom it was determined showed some degree of reversibility of the electroencephalogram with administration of oxygen and during the phasic changes of Cheyne-Stokes respiration. These reversible changes will be discussed in another paper.[13] As indicated previously, electroencephalographic changes of stage IV need not be irreversible, although it is always associated with the more severe disturbances in awareness.

Although postmortem examination was performed on 13 of the 16 patients of the total series, it is not our purpose in this paper to discuss the histologic changes in the brain. Moreover, in many instances death occurred some time after the period of clinical study. Further, the neuropathologic examination was not adequate for careful evaluation. In 1 patient, however (group 3, case 25, with a diagnosis of dermatomyositis), the brain showed minute focal areas of gliosis, probably secondary to disease of the smaller vessels, which undoubtedly had been present to some degree at the time of clinical study.

Group VI.—These 9 patients who experienced varying degrees of delirium were examined once. Circumstances beyond our control prevented reexamination.

CASE 45.—*H. W., a woman aged 73. Arteriosclerotic heart disease; previous myocardial infarction; chronic congestive heart failure (four years). Duration of delirium before first examination unknown. Admission, Oct. 27, 1941.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
10/29	Moderate	V	Venous pressure 170 mm. of water, with increase on compression of liver to 300 mm.; circulation time 52 sec.

13. Engel, G. L., and Romano, J.; Studies of Delirium: II. Reversibility of the Electroencephalogram with Experimental Procedures, Arch. Neurol. & Psychiat., this issue, p. 378.

CASE 46.—*M. H., a man aged 64. Coronary occlusion; congestive heart failure. Duration of delirium before first examination, three weeks. Admission, March 19, 1942.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
4/10	Mild	I-II	Delirium more severe during first 10 days of hospitalization, greatly improved on 4/10/42. Venous pressure 85 mm. of water; circulation time 25 sec.; oxygen saturation of arterial blood 98%

CASE 47.—*C. W., a man 71. Arteriosclerotic heart disease; congestive heart failure. Duration of delirium before first examination, six weeks (?). Admission, Sept. 25, 1941.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
10/8	Severe	II	Cheyne-Stokes respiration; circulation time 15 sec.

CASE 48.—*B. K., a man aged 64. Chronic bronchitis; asthma; emphysema. Duration of delirium before first examination unknown. Admission, Oct. 11, 1941.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
10/17/41	Moderate	IV-V	Oxygen saturation of arterial blood 86%

CASE 49.—*G. Y., a man aged 67. Chronic bronchitis; asthma; emphysema; acute infection of upper respiratory tract. Duration of delirium before first examination, two days. Admission, Dec. 21, 1941.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
12/23/41	Mild	II	Patient recovering from severe acute attack of asthma

CASE 50.—*F. S., a man aged 61. Asthma; bronchitis; emphysema. Duration of delirium before first examination unknown. Admission, Dec. 2, 1942.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
12/8	Mild	I	Oxygen saturation of arterial blood, 78%

CASE 51.—*B. F., a man aged 65. Asthma; bronchitis; emphysema; bilateral bronchopneumonia. Duration of delirium before first examination, three weeks. Admission Feb. 25, 1942.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
3/10	Moderate	I	Progressive clinical improvement in week preceding study

CASE 52.—*J. F., a man aged 57. Chronic alcoholism; gastritis. Duration of delirium before first examination, two months. Admission Feb. 23, 1942.*

Date	Disturbance in Awareness	Electroencephalographic Stage	Comment
2/26	Moderate	III (?)	Excessive drinking for past 2 mo.; history of addiction to alcohol for 20 yr. or more

DELIRIUM

II. REVERSIBILITY OF THE ELECTROENCEPHALOGRAM WITH EXPERIMENTAL PROCEDURES

GEORGE L. ENGEL, M.D.,* AND JOHN ROMANO. M.D.

CINCINNATI

The electroencephalographic changes associated with delirium have been presented in a previous report.[1] These changes were observed to be reversible to the extent to which the delirium was reversible. The character of the electroencephalographic changes was determined by the intensity, duration and reversibility of action of the noxious factors as modified by the essential premorbid integrity of the central nervous system.

In this report further data will be presented to illustrate the reversibility of the electroencephalogram during experimental procedures designed to modify some of the basic physiologic derangements. The effects studied included those of (a) inhalation of oxygen, (b) changes in posture, (c) phases of Cheyne-Stokes respiration. (d) blood transfusion, (e) administration of adrenal cortex substances and (f) infusion of dextrose.

MATERIAL AND METHODS

Twenty-five patients were studied. Clinical and laboratory observations on these patients, as well as the psychologic and electroencephalographic methods of examination and interpretation, are presented in a previous report.[1]

The method of quantitative analysis of the electroencephalogram and the classification of the degrees of electrical abnormality as stages I to V have already been described.[1] These five stages may again be summarized.

Stage I: Predominance of normal, regular frequencies with a small amount of regular and irregular slow frequencies (5 to 7 per second). There is generally some decrease in regularity of the record as a whole.

Stage II: Further decrease in regularity of the entire record, which now contains only a moderate amount of normal, regular frequencies. There is an increase both in low voltage fast activity and in regular and irregular slow (4 to 7 per second) frequencies.

Stage III: Predominantly low voltage fast activity with some regular and irregular slow frequencies (3 to 6 per second) and relatively little activity in the normal range of frequencies.

Stage IV: Completely disorganized, irregular record with a dominant slow pattern (2 to 7 per second), variable small amounts of low voltage fast activity and no recognizable alpha activity (8 to 12 per second). At this stage the record frequently shows groups of high voltage very slow waves ($\frac{1}{2}$ to 3 per second) recurring in a rhythmic fashion. Low voltage fast activity is sometimes superimposed on these slow waves.

Stage V: Rather regular slow activity (3 to 7 per second) of moderately high voltage with few or no normal frequencies.

Stages III, IV and V are not influenced by the subject's opening or closing the eyes.

In addition, as further criteria for comparison of consecutive tracings under different conditions, the total amount of 8 to 12 per second activity and the dominant frequency of each record were noted. The dominant frequency was the frequency representing 50 per cent or more of the total record. When no frequency accounted for 50 per cent of the record, the most common frequencies which together made up 60 per cent of the total were taken as dominant.

The following arbitrary criteria were used as measures of the significance of the changes observed in the electroencephalogram during the experimental procedures:

1. The change in the electroencephalographic pattern was considered definitely significant when two or more of the following features were present: (a) change in stage, (b) shift in dominant frequency or (c) a change of more than 20 in the percentage of 8 to 12 per second activity.

2. The alteration in the electroencephalographic pattern was regarded as probably significant when the following features were present: (a) no change in stage, but (b) a shift in dominant frequency and (c) a change of from 10 to 20 in the percentage of 8 to 12 per second activity.

3. A shift in dominant frequency alone, a change in the total amount of 8 to 12 per second activity alone or a shift in dominant frequency with a change of less than 10 in the percentage of 8 to 12 per second activity were considered as not significant.

INHALATION OF OXYGEN

Experimental Results. — Electroencephalographic tracings were taken in a total of 20 experiments before, during and occasionally after oxygen was administered by mask to 9 patients with cardiac decompensation and to 4 patients with pulmonary decompensation. The results

sodes of delirium it was not possible to differentiate the records of these 5 patients from those of any other delirious patients. Williams [5c] was unable to predict the development of post-traumatic epilepsy from the appearance of the electroencephalograms obtained after acute injuries to the head.

Analysis of the psychologic data reveals a direct correlation between the electrical abnormality and the primary psychologic symptom in delirium, i. e., the disturbance of consciousness. There was far less correlation between the electrical abnormality and the more personal aspects of behavior, namely, the character and expression of anxiety, the content of thought and the nature of sense deceptions. It must be emphasized that while this correlation with disturbances in consciousness was clear, the mere coincidence of these psychologic disturbances and electroencephalographic abnormalities does not in itself establish a cause and effect relation. More complete knowledge of the basic mechanisms responsible for normal and abnormal electrical activity must be acquired before conclusions are drawn concerning the association of characteristic electrical patterns with various types of psychologic behavior. Furthermore, we believe that in future electroencephalographic studies of patients with psychologic disturbances the presence or absence of disturbances in consciousness must be considered before other correlations with behavior are attempted. The mere presence of abnormal brain waves in the electroencephalogram of a person with disturbances of behavior does not establish a relation between the two. In a case of epilepsy, for example, the abnormal record of the interseizure period may be unassociated with any disturbances in behavior, while the immediately postseizure period may be accompanied by conspicuous disturbances in consciousness and confusion.

From a clinical point of view, there is usually no need to utilize the electroencephalogram in the diagnosis of delirium. Simple psychologic tests, designed to evaluate the awareness or attention of a patient, are adequate. However, the method may be of aid in clinical confirmation, in evaluation of the degree of physiologic restoration and in following the course of specific therapy. Further, the method has great value in experimental physiologic studies of spontaneous and induced deliriums.

SUMMARY

Psychologic and electroencephalographic studies of 53 patients with delirium of varying cause, intensity and duration revealed electroencephalographic abnormalities in all patients who had disturbances in consciousness. These changes were found to be reversible to the extent to which the clinical delirium was reversible. The character of the electroencephalographic change appeared to be independent of the specific underlying disease process but was directly related to the intensity, duration and reversibility of the noxious factors, as modified by the basic physiologic status of the body. A correlation was established between the electrical abnormality and the primary psychologic symptom in delirium, i. e., the disturbance of consciousness, but there was far less correlation with the more personal aspects of behavior, namely, the character and expression of anxiety, the content of thought and the nature of sense deceptions.

Cincinnati General Hospital.

the carbon dioxide content rose slightly and in 1 it was unchanged (table 1).

Of the 10 electroencephalograms (obtained from 8 patients) showing definite improvement during administration of oxygen, 4 represented stage IV before inhalation of oxygen; 1, stage III; 3, stage III to stage II; 1, stage II, and 1, stage II to I. The electroencephalograms of 5 of these 8 patients showed partial or complete restoration to normal with recovery from the

significance. Four patients had congestive heart failure. Two patients (K. T., case 2, and J. Mc., case 27) had each shown definite improvement in the electroencephalogram on one other occasion— K. T. at stage IV, but to a less striking degree at stages II and I. J. Mc. showed decreasing improvement as the electroencephalogram shifted toward stage V. Arterial blood was studied in 4 experiments. Oxygen saturation was normal in 3 determinations and low (80 per cent) in
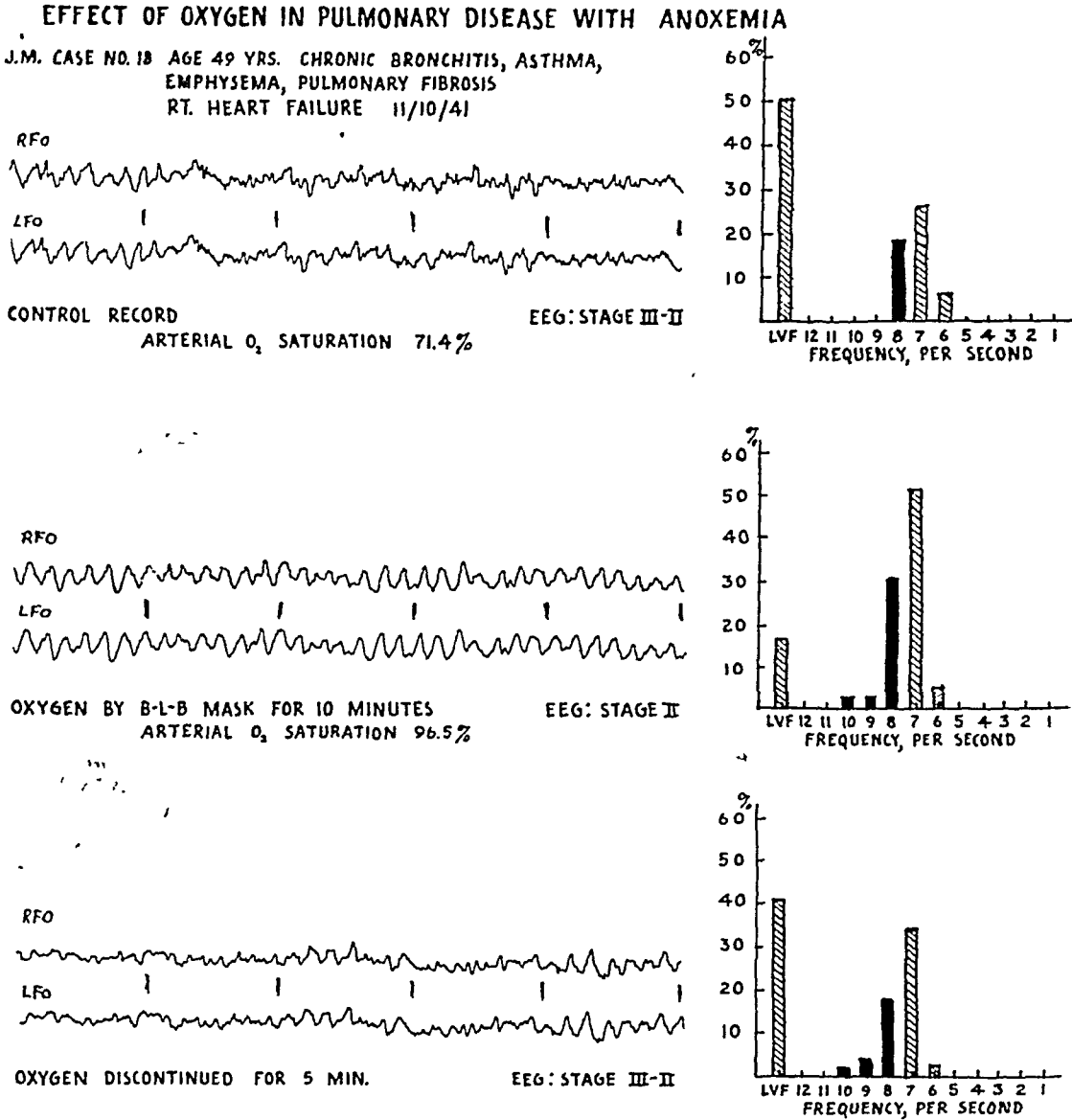
Fig. 2.—With an oxygen saturation of arterial blood of 71.4 per cent, the electroencephalogram showed predominant low voltage fast activity mixed with 6 to 8 per second activity (stage II to III). After oxygen was inhaled for ten minutes, the oxygen saturation of arterial blood rose to 96.5 per cent, and the electroencephalogram showed dominant 7 per second activity (stage II). With interruption of inhalation of oxygen, the record returned toward the original pattern.

acute disease process. The electroencephalogram of 1 patient changed from stage IV to stage V, and a considerable degree of dementia persisted. The 2 remaining patients were examined only once.

In 7 experiments on 5 patients the improvement in the electroencephalographic pattern was considered to be of probable, but not definite,

1 determination. With inhalation of oxygen it rose to 98 per cent or above in all instances. The carbon dioxide contents of arterial blood were not remarkable and showed no significant changes. The electroencephalograms before the administration of oxygen represented stage IV in 3 experiments and stage V, stage II and stage I respectively in 1 experiment each.

are recorded in table 1 and typical cases are illustrated in figures 1 and 2.

According to the criteria of change already outlined, the electroencephalogram showed definite improvement in 10 experiments, probable improvement in 7 experiments and no improvement in 3 experiments.

Of the patients showing definite improvement, 5 had cardiac failure (6 experiments) and 3 chronic pulmonary disease (4 experiments). Three determinations of the oxygen and carbon

per cent) and carbon dioxide content (43.22, 39.9 and 48.1 volumes per cent respectively) of arterial blood. In all patients inhalation of 100 per cent oxygen resulted in an increase in oxygen saturation of arterial blood to above normal (103, 104 and 105 per cent respectively), while in 2 patients the carbon dioxide content of arterial blood fell slightly and in 1 it was unchanged. In all the patients with pulmonary disease who showed definite improvement in the electroencephalographic pattern the oxygen saturation of arterial
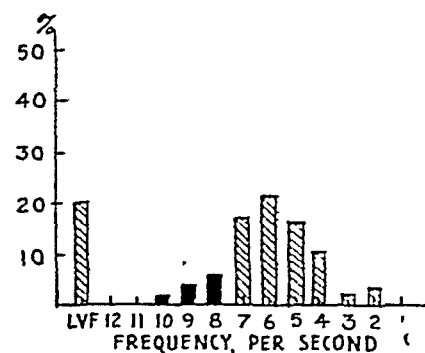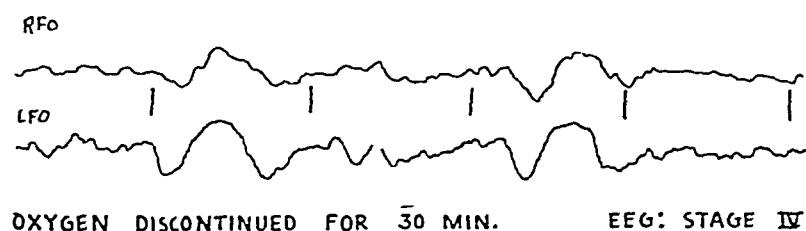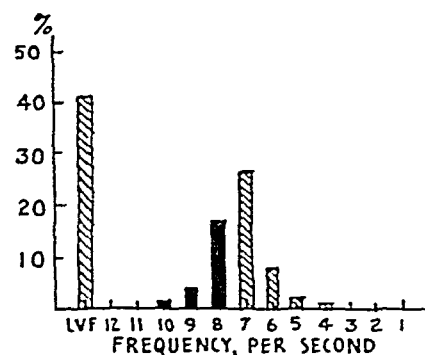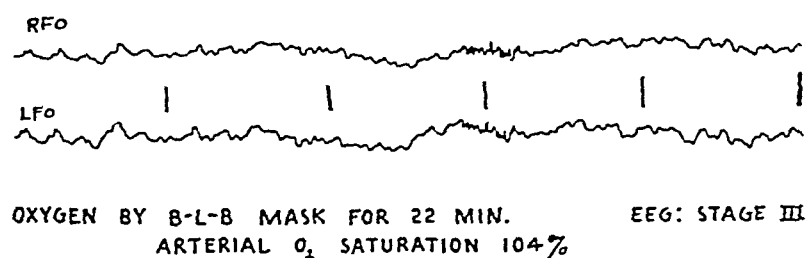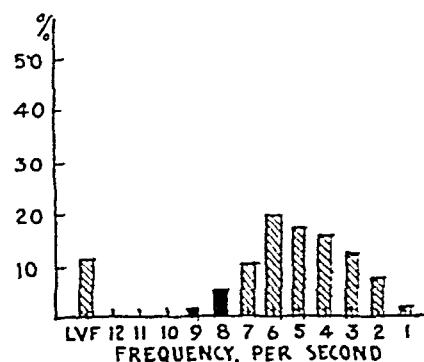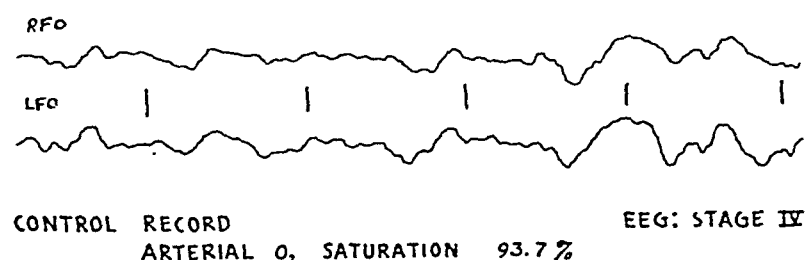
Fig. 1.—The electroencephalogram shifted from stage IV to stage III during administration of oxygen and then returned to stage IV thirty minutes after the use of oxygen was discontinued. The spectrum analysis of three hundred second samples is presented on the right. The oxygen saturation of arterial blood was 93.7 per cent during the first run and 104 per cent during administration of oxygen.

dioxide contents of arterial blood were made on the patients with heart disease and 4 determinations on the 3 with pulmonary disease. All the patients with cardiac decompensation had normal values for oxygen saturation [2] (96, 93.7 and 95.5

blood was below normal (69, 71.4, 87.3 and 88.5 per cent), while the carbon dioxide content was high (62.6, 58.2, 54.1 and 55.5 volumes per cent). In all these patients the oxygen saturation of arterial blood rose to normal or above normal during inhalation of oxygen while in 2 patients

2. The values were not corrected for the amount of oxygen dissolved in the plasma. Oxygen saturations of arterial blood of over 100 per cent may result when this correction is not made. Since oxygen dissolved

in plasma is available for metabolic needs, it is properly included in studies of this nature.

The fifth patient of the group who showed probable improvement in the electroencephalogram had chronic pulmonary disease and at the time of study had mild anoxemia (oxygen saturation arterial of blood 86.8 per cent). The electroencephalogram was of stage IV to stage V type. Inhalation of oxygen resulted in some increase in the amount of 8 to 12 per second activity and a slight shift toward a faster dominant frequency. This patient was examined only once.

Inhalation of oxygen failed to affect the electroencephalograms of 3 patients. Two of these patients had congestive heart failure. One of them was semistuporous at the time of examination; the electroencephalogram was of extreme stage IV type, and the patient died the

instances it was obvious that the patient was brighter and more alert immediately after the mask was removed.

Summary.—During the administration of oxygen to 9 patients with congestive heart failure and to 4 patients with pulmonary decompensation (20 experiments), the electroencephalogram showed definite improvement in 10 experiments probable improvement in 7 experiments and no significant change in 3 experiments. The patients with congestive heart failure showed electroencephalographic improvement in spite of the fact that the oxygen saturation of arterial blood was normal before administration of oxygen. However, these patients generally showed a rise in oxygen saturation to over 100 per cent. The patients with chronic pulmonary

TABLE 2.—*Effect of Posture in Cases of Congestive Heart Failure on the Electroencephalogram*

Name, Sex, Age, Yr.	Case No.	Diagnosis	Date	Electroencephalogram						Comment
				Sitting Position			Recumbent Position			
				Stage	Percentage 8-12 per Sec. Frequency	Dominant Frequency	Stage	Percentage 8-12 per Sec. Frequency	Dominant Frequency	
L. S. M 60	14	Arteriosclerotic heart disease; congestive heart failure	1/20	III	13	LVF	IV	6	5-7 per sec. LVF	Patient recumbent 18 min. circulation time 53 sec. (dehydrocholic acid); venous pressure 180 mm. of water, with rise on compression of right upper quadrant to 230 mm.
W. F. M 54	15	Acute coronary occlusion; congestive heart failure	10/2	III	22	LVF	IV	20	LVF 5-7 per sec.	Patient recumbent 30 min.; circulation time 43 sec. (dehydrocholic acid); venous pressure 180 mm. of water
H. W. F 73	45	Arteriosclerotic heart disease; chronic congestive heart failure	10/29	V	31	6-8 per sec.	V	22	7-8 per sec.	Patient recumbent 7 min.; circulation time 52 sec. (dehydrocholic acid); venous pressure 170 mm. of water, with rise on compression of right upper quadrant to 300 mm. of water

following day. The second patient had chronic congestive heart failure, and the degree of disturbance in the level of awareness was essentially unchanged since the first examination, four months earlier. The electroencephalogram was of stage V type. No studies in the gases of the blood were carried out on these 2 patients. The third patient (G. A., case 19) had pulmonary disease. He had a stage III electroencephalogram on first examination, and the oxygen saturation of arterial blood rose from 79 to 101 per cent during the inhalation of oxygen. On two subsequent occasions inhalation of oxygen resulted in definite improvement in the electroencephalogram. It is possible that the criteria necessary to show changes within stage III (dominant low voltage fast activity) are inadequate.

Because of the presence of the oxygen mask, it was not possible to test the mental status during inhalation of oxygen. However, in many

disease all had cyanosis and anoxemia, and administration of oxygen raised the oxygen saturation of arterial blood to normal levels or higher. Improvement was demonstrable at all stages (1 to V) of the electroencephalogram but was least noticeable at stage V. On the whole, the improvement during administration of oxygen was greatest for patients whose delirium was of recent origin and who showed eventual restoration to normal, or near normal, of both the electroencephalogram and the mental status. The changes occurring in the electroencephalogram during use of oxygen were identical with those appearing spontaneously some days or weeks later, during the course of recovery from the underlying disease.

CHANGES IN POSTURE

Because patients with congestive heart failure become more dyspneic and cyanotic when recumbent than when sitting, the effect on the electro-

TABLE 1.—*Effect of Administration of Oxygen in Cases of Congestive Heart Failure and Pulmonary Insufficiency on the Electroencephalogram*

Name, Sex, Age, Yr.	Case No.	Diagnosis	Date	Electroencephalogram — Stage			Percentage of Frequency, 8-12/Sec.			Dominant Frequency/Sec.*			Arterial Oxygen Saturation, %		Arterial Carbon Dioxide Content, Vol.%		Electroencephalographic Improvement	Comment
				Before	During	After	Before	During	After	Before	During	After	Before	During	Before	During		
L.S. M 60	14	Arteriosclerotic heart disease; congestive heart failure	1/20	IV	III	..	6	25	..	5-7 LVF	LVF	...	96.0	103	43.2	41.5	Definite	
			1/26	IV	III	IV	6	22	10	3-6	LVF 7	5-7 LVF	93.7	104	39.9	37.4	Definite	Moderately severe left ventricular failure; Cheyne-Stokes respiration
O.W. M 71	47	Arteriosclerotic heart disease; congestive heart failure	10/8	II	I	..	37	67	..	7-8	8-9	...	....	...	...	...	Definite	Severe congestive heart failure; Cheyne-Stokes respiration
W.F. M 54	15	Acute coronary occlusion; congestive heart failure	10/2	III	III-II	..	20	44	..	LVF 7	7-8 LVF	...	....	...	...	...	Definite	Moderately severe left ventricular failure
K.T. F 61	2	Hypertensive heart disease; congestive heart failure	12/29	IV	IV	..	17	39	..	2-7	6-8 LVF	...	....	...	...	...	Definite	Minimal left ventricular failure
			1/5	II	II-I	..	38	50	..	6-8	7-9	...	....	...	...	...	Probable	Minimal left ventricular failure
			1/7	I	I	..	56	69	..	8-9 LVF	8-9	...	....	...	...	...	Probable	
J.Mc. M 74	27	Congestive heart failure; pneumonia; empyema; cirrhosis of liver; jaundice	12/24	IV	IV	IV	9	23	25	4-7	6-8	6-8	94.2	...	45.1	...	Probable	Severe left and right ventricular failure; jaundice
			12/30	IV	V	V	7	33	25	5-7	7-9	6-8	95.5	105	48.1	48.1	Definite	Heart failure less severe; jaundice less; empyema
			1/15	V	V	..	15	28	..	5-7	6-8	...	94.7	105	48.7	48.7	Probable	Moderately severe congestive heart failure; empyema; jaundice
E.O. F 53	35	Rheumatic heart disease; mitral stenosis and mitral insufficiency; congestive heart failure; thrombosis of superior vena cava, left internal jugular and left subclavian veins	11/19	IV	IV	..	3	14	..	3-6	6-8	...	91.2	99.3	38.0	38.1	Probable	
A.O. F 55	13	Hypertensive heart disease; congestive heart failure	4/27	IV	IV	..	9	20	..	5-7	6-8	...	80.0	98.2	49.6	51.5	Probable	Before inhalation: arterial-internal jugular venous oxygen difference 8.52 vol.%. During inhalation: arterial-internal jugular venous oxygen difference 12.66 vol.%
S.F. F 54	24	Rheumatic heart disease; chronic congestive heart failure	1/6	V	V	..	30	33	..	6-8	7-8	...	...	...	...	...	None	Severe failure
R.B. F 73	36	Hypertensive heart disease; complete heart block; congestive heart failure	3/24	IV	IV	..	0	0	..	3-4	4-5	...	....	...	...	...	None	Venous pressure 205 mm. water; circulation time 45 sec.
E.A. M 67	37	Chronic bronchitis; asthma; emphysema; right and left ventricular failure	2/19	III-II	II	..	12	34	..	0-7	7-8	...	69.0	...	62.6	...	Definite	Arterial-internal jugular venous oxygen difference 2.86 vol.%; internal jugular venous carbon dioxide content 65.3 vol.%
G.A. M 60	19	Chronic bronchitis; asthma; emphysema; right ventricular failure	12/3	III	III	..	43	42	..	LVF	LVF	...	79.0	101.0	59.2	59.6	None	Arterial-internal jugular venous oxygen difference 5.45 vol.%
			12/16	III-II	II	II	43	80	34	6-9	8-10	6-9	87.3	101.8	54.1	53.5	Definite	
J.M. M 49	18	Chronic bronchitis; asthma; emphysema; pulmonary fibrosis; failure of right side of heart	12/19	II-I	I	III-II	66	83	..	7-9 LVF	9-10	LVF, 7	85.5	101.0	55.5	57.6	Definite	
			11/10	III-II	II		18	32	23	LVF	7-8		71.4	96.5	58.2	60.0	Definite	
B.K. M 64	48	Chronic bronchitis; asthma; emphysema	10/17	IV-V	IV-V	..	16	27	..	6-7	6-8	...	86.8	...	...	...	Probable	

* In this table, and in the accompanying tables, LVF indicates low voltage fast activity.

more normal pattern in the hyperpneic phase and reversing to a more abnormal one in the apneic phase. All these patients had cardiac disease: Three had moderate congestive heart failure, and 1 was recovering from congestive heart failure at the time of examination. Three of the patients had stage IV electroencephalograms, and 1 had a stage II encephalogram during the apneic phase.

Two patients showed no significant difference in the electroencephalograms taken during the

hind the changes in respiration. This is clear on gross inspection of figure 4, in which the beginning restlessness is marked by the superimposition of muscle potentials on the electroencephalogram. This lag suggests that both the changes in cortical potentials and those in consciousness are secondary to the alterations in respiration. It explains, perhaps, our failure to demonstrate a difference in spectrum analyses between the hyperpneic and the apneic phase in the 2 patients with the most abnormal electroencephalograms.

TABLE 3.—*Effects of Phasic Changes of Cheyne-Stokes Respiration on the Electroencephalogram*

Name; Sex; Age, Yr.	Case No.	Date	Diagnosis	Apneic Phase			Hyperpneic Phase			Comment
				Stage	Percentage 8-12 per Sec. Frequency	Dominant Frequency (per Sec.)	Stage	Percentage 8-12 per Sec. Frequency	Dominant Frequency (per Sec.)	
M. B. F 68	34	2/17	Myocardial infarction; acute congestive heart failure	IV	6	5 6	IV	27	6 8	Venous pressure 190 mm. of water; circulation time 26 sec.
W. F. M 54	15	10/2	Myocardial infarction; acute congestive heart failure	IV	23	5-7	II	42	7-8	Venous pressure 180 mm. of water; circulation time 43 sec.
C W. M 71	47	10/8	Arteriosclerotic heart disease	II	37	6 8	II-I	58	7-8	Circulation time 15 sec.
O. M. M 72	43	2/24	Myocardial infarction; embolic (?) hemiplegia	IV	17	5-7	III-II	42	7-8 and LVF	
F. G. M 84	39	1/9	Obstructive jaundice; left ventricular failure	IV	3	4-6	IV	1	2-5	Congestive heart failure on admission (1/2/42) but not at time of examination; icteric index 108
W. F. M 46	26	1/19	Malignant hypertension; uremia; hypertensive encephalopathy	IV	0	2-4	IV	0	3-5	Blood pressure 240/165; cerebrospinal fluid pressure 410 mm. of water; nonprotein nitrogen of blood 73 mg./100 cc.; venous pressure elevated; pulmonary congestion

TABLE 4.—*Effect of Transfusion of Whole Blood in a Case of Severe Anemia*

Name; Sex; Age, Yr.	Case No.	Date	Hemoglobin, Gm./100 Cc.	Red Blood Cells	Arterial Oxygen Saturation, %	Arterial Oxygen Content, Vol. %	Internal Jugular Venous Oxygen Content, Vol. %	Arterio-venous Oxygen, Difference, Vol. %	Mental Status	Electroencephalogram		
										Stage	Percentage 8-12 per Sec. Frequency	Dominant Frequency (per Sec.)
A. P. F 74	4	4/ 9/42	2.5	630,000	100	5.30	2.65	2 65	Moderate confusion	II	11	6-7
		4/11/42	5.8	1,660,000	102	10.03	5.62	4.41	Mild confusion	I to normal	72	8

two phases of Cheyne-Stokes respiration. One patient had obstructive jaundice and hypercholemia and had recovered from congestive heart failure. The second patient had malignant hypertension and uremia. Both had stage IV electroencephalograms, and it is perhaps significant that the records for both showed extremely slow dominant frequencies and no (0 to 3 per cent) frequencies in the 8 to 12 per second range.

All 6 patients showed obvious fluctuations in awareness during the alternating phases of respirations. However both the changes in the level of consciousness and the alterations in the electroencephalogram appeared to lag somewhat be-

Since 1 of these patients (W. F., case 26) subsequently improved clinically (although he eventually died), lack of essential reversibility cannot be invoked as the explanation.

BLOOD TRANSFUSION

In chronic anemia due to inadequate hematopoiesis [3] or to chronic loss of blood without other

3. Pernicious anemia obviously cannot be included with these anemias, since there is much evidence that it is a deficiency disease involving more than blood formation alone. Indeed, it is well known that delirium may develop with only moderate anemia, and may even become worse while the blood count is rising.

encephalogram of changes in posture was studied in 3 such patients. The results are summarized in table 2, and a typical case is illustrated in figure 3. All the patients had severe congestive heart failure at the time of study, as was evidenced by prolonged circulation time and high venous pressure. In 2 instances after the patients had been recumbent for eighteen to thirty minutes, the electroencephalogram became definitely more abnormal. Both patients had stage III electroencephalograms when they were sitting,

tal statuses in the two positions were not compared.

## PHASIC CHANGES ASSOCIATED WITH CHEYNE-STOKES RESPIRATION

All clinicians are familiar with the patient with Cheyne-Stokes respiration who fluctuates between stupor and confused agitation during the phasic changes in respiration. It is of interest to study the electroencephalogram during these fluctuations. Electroencephalographic studies were

EFFECT OF POSTURE IN CONGESTIVE HEART FAILURE

L.S. CASE NO. 14 AGE 60 YRS. ARTERIOSCLEROTIC HEART DISEASE
CONGESTIVE HEART FAILURE 1/20/42

SITTING   EEG: STAGE III
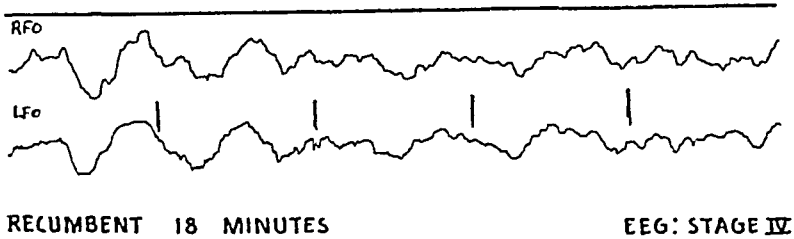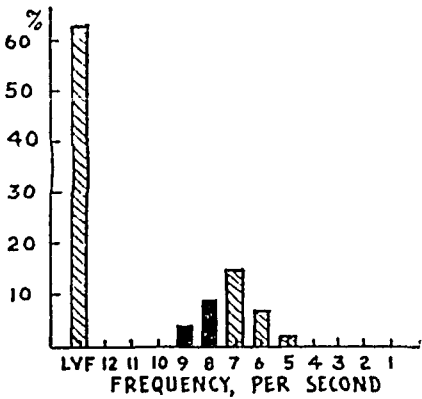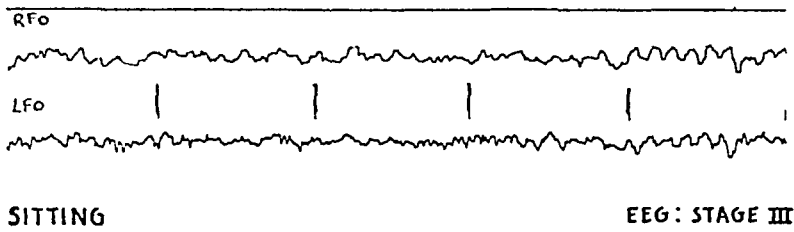
RECUMBENT 18 MINUTES   EEG: STAGE IV
VENOUS PRESSURE 180 MIN. H_2O
RISE ON R.U.Q COMPRESSION TO 230 MIN. H_2O
CIRCULATION TIME, (DEHYDROCHOLIC ACID), 53 SEC.
ARTERIAL O_2 SATURATION 96 %
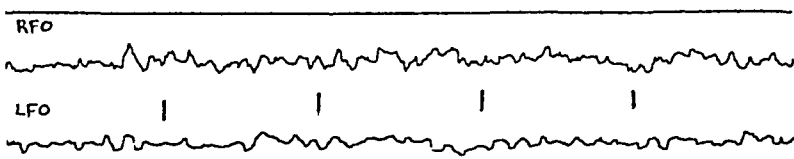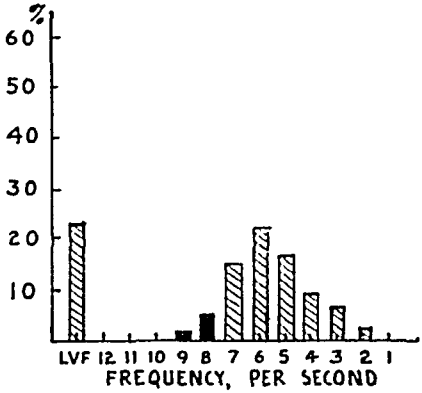
RECUMBENT 30 MINUTES, O_2 BY B-L-B   EEG: STAGE III
MASK FOR 10 MINUTES
ARTERIAL O_2 SATURATION 105 %
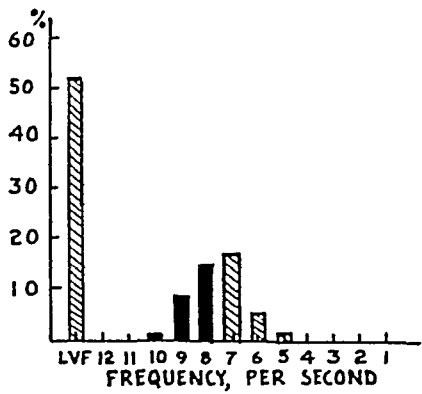
Fig. 3.—After the patient had been eighteen minutes in the recumbent position, the electroencephalogram shifted to stage IV, from the control phase of stage III when he was in the sitting position. Administration of oxygen, with the patient in the recumbent position, led to improvement in the electroencephalogram (stage III).

which shifted to stage IV patterns when they were recumbent. The electroencephalogram of the third patient showed a moderate change in a similar direction with a postural change of seven minutes' duration. This patient had chronic heart failure, and the electroencephalogram represented stage V, the phase of chronic damage. All 3 patients were obviously more dyspneic, cyanotic and uncomfortable in the recumbent position; the men-

made on 6 patients with Cheyne-Stokes respiration during the alternating phases of respiration (table 3). A total run of three hundred seconds of electroencephalographic record was analyzed for each phase. A typical complete cycle is illustrated in figure 4.

With 4 patients the electroencephalograms showed a definite and significant difference for the two respiratory phases, shifting toward a

complications, the reduction in hemoglobin must be profound before the oxygen supply to the brain is impaired. Greatly increased cerebral circulation generally compensates for the reduction in oxygen-carrying capacity of the blood.

Electroencephalographic and psychologic data were obtained from a patient suffering from severe and chronic anemia, probably aplastic, before and after she received 1,000 cc. of blood. The patient had normal blood pressure and had never been in shock. The data for this patient are summarized in table 4, and the electroenceph-

after this procedure. It is reasonable to ascribe this improvement to the increased oxygen-carrying capacity of the blood, since it is unlikely that the cerebral blood flow increased.

ADMINISTRATION OF ADRENAL CORTEX EXTRACT AND DEXTROSE TO PATIENTS WITH ADDISON'S DISEASE

Abnormal electroencephalograms have been reported for patients with Addison's disease in all stages of therapy.[4] Intensive observations on 2 patients afforded an opportunity to study the

EFFECT OF BLOOD TRANSFUSION IN SEVERE ANEMIA

A.P. CASE NO. 4 AGE 74 YRS.
ANEMIA, CAUSE UNKNOWN

4/9/42 BEFORE TRANFUSION, Hgb. 2.5Gm.; RBC, 630,000/cu.mm. EEG: STAGE II
ARTERIAL O₂ CONTENT, 5.30 VOL.%

4/11/42 AFTER 1000 cc BLOOD TRANFUSION
Hgb., 5.8Gm; RBC, 1,660,000/cu. mm.
ARTERIAL O₂ CONTENT, 10.05 VOL.%

EEG: I-NORMAL
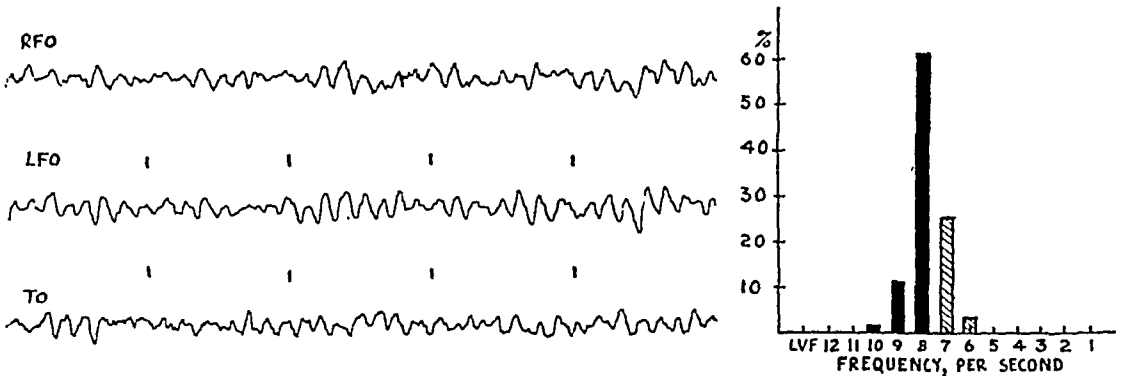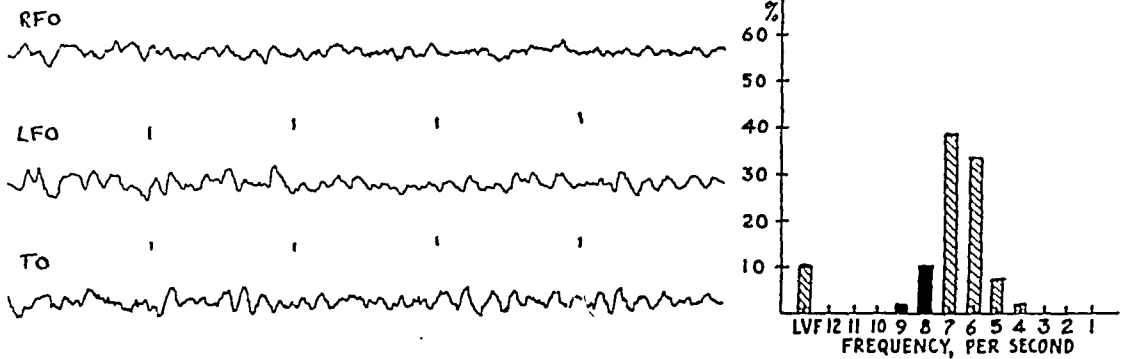
Fig. 5.—Elevation of the red blood cell count from 630,000 to 1,660,000 per cubic millimeter resulted in improvement in the electroencephalogram and in the mental status.

alographic changes are illustrated in figure 5. With an initial hemoglobin concentration of 2.5 Gm. per hundred cubic centimeters and a red blood cell count of 630,000 per cubic millimeter, the difference in oxygen content between arterial and internal jugular venous blood was only 2.65 volumes per cent. After a transfusion of 1,000 cc. of blood, the oxygen-carrying capacity of the blood was doubled and the arteriovenous oxygen difference increased to 4.41 volumes per cent. There was a significant improvement both in the electroencephalogram and in the mental status

electrical activity of the brain during an addisonian crisis and during treatment with desoxy-

4. (a) Engel, G. L., and Margolin, S.: Neuropsychiatric Disturbances in Addison's Disease and Role of Impaired Carbohydrate Metabolism in the Production of Abnormal Cerebral Function, Arch. Neurol. & Psychiat. 45:881 (May) 1941; (b) Neuropsychiatric Disturbances in Internal Disease: Metabolic Factors and Electroencephalographic Correlations, Arch. Int. Med. 70:236 (Aug.) 1942. (c) Hoffman, W. C.; Lewis, R. A., and Thorn, G. W.: The Electroencephalogram in Addison's Disease, Bull. Johns Hopkins Hosp. 70: 335, 1942.

Fig. 4.—One complete respiratory cycle is illustrated, while the frequency spectrums are the result of analyses of three hundred second samples of each phase. During the apneic phase the patient was stuporous. During the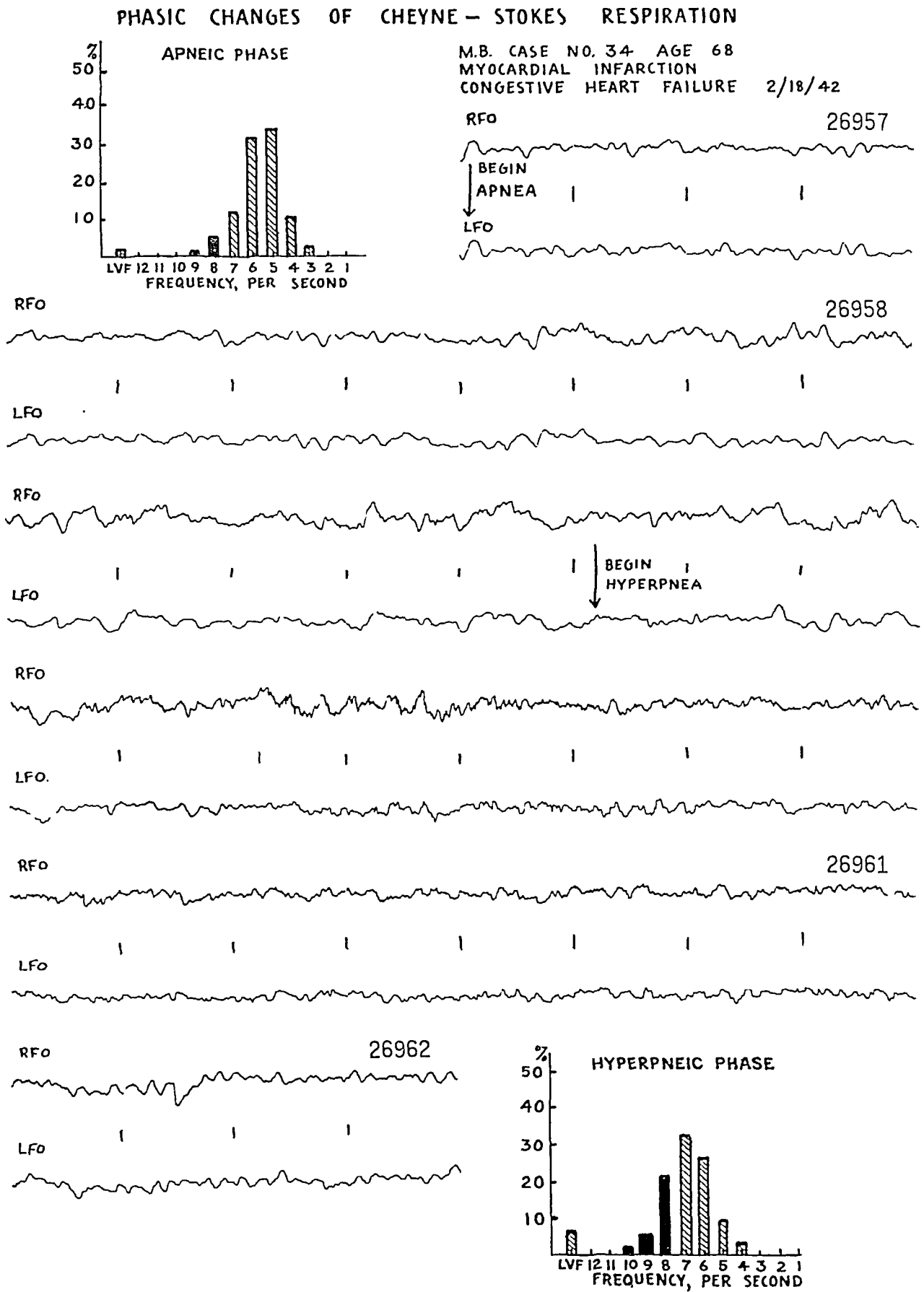 hyperpneic phase she became more active, as evidenced by the appearance of muscle potentials in the electroencephalogram.

Name; Sex; Age; Yr.	Case No.	Date	Treatment	Time	Electroencephalogram — Stage	Per-centage 8-12 per Sec. Fre-quency	Domi-nant Fre-quency (per Sec.)	Intra-venous Dextrose Toler-ance Test, Mg./ 100 Cc.	Comment
		3/31	1 mg. of desoxycortico-sterone acetate intramus-cularly and 6 Gm. sodium chloride and 12 mg. riboflavin orally daily	Fasting	I	66	7-9	73	Sodium 137 mEq./L.; chloride 110 mEq./L.; condition good
				End of infu-sion	I	52	7-8	210	
				1 hour	I	55	7-8	106	
				2 hours	..	..	...	63	
				2½ hours	I-II	37	6-8	60	Hypoglycemic reaction
				3 hours	II	32	5-8	53	
		4/4	15 cc. adrenal cortex ex-tract intramuscularly daily for 4 days; 47.5 cc. adrenal cortex extract on fifth day	Fasting	I	61	7-8	81	Condition good
				End of infu-sion	I	61	7-8	224	
				1 hour	I	72	8-9	128	
				2 hours	I	58	7-8	106	
				2½ hours	I-0	81	8-9	75	
				3 hours	I-0	86	8-9	74	No hypoglycemic reaction
				3½ hours	I-0	90	8-10	74	
				1 hour (oral)	I	50	7-8	122	

corticosterone acetate and aqueous adrenal cortex extract, given separately and in combination. The electroencephalograms were generally obtained with the patient in the fasting state and during tolerance tests for dextrose given intravenously. The encephalographic data may be summarized as follows:

1. The electroencephalograms of both patients were most abnormal during the addisonian crisis, and with clinical improvement, regardless of the type of therapy used, the electroencephalogram improved (fig. 6).

2. Treatment with desoxycorticosterone acetate sufficient to produce an optimum clinical response resulted in improvement in the electroencephalogram but never in complete restoration to normal. One patient (R. W., case 22) was studied eight times during a six month period of treatment with desoxycorticosterone acetate and sodium chloride. The electroencephalogram showed maximum improvement in a few weeks and thereafter presented no essential change while the patient was receiving this form of treatment. It will be recalled that desoxycorticosterone acetate is effective in correcting the disturbances in electrolytic balance and in blood pressure but is without effect on carbohydrate metabolism. These results are in agreement with previous data.[4b,c]

3. The addition for a month at a time of individual members of the vitamin B complex group (thiamine, nicotinamide, riboflavin and calcium pantothenate) to the desoxycorticosterone acetate and sodium chloride therapy of patient R. W. (case 22) did not influence the electroencephalogram or the tolerance for dextrose. This is in accord with the data of Hoffman and associates.[4c]

4. Large quantities of aqueous adrenal cortex extract (Upjohn)[5] were most effective in producing improvement in the electroencephalogram. The patients were given 100 cc. of the extract in five to seven days (see table 5 for exact schedule).

In the case of E. Mc. (case 21), to whom a total of 20 mg. of desoxycorticosterone acetate was given in addition to the adrenal cortex extract, the electroencephalogram became entirely normal. During the next ten days the patient was treated with desoxycorticosterone alone. During this period, however, the temperature was elevated, and signs of activation of pulmonary tuberculosis appeared. The electroencephalogram became more abnormal. Treatment with 100 cc. of the adrenal cortex extract over five days now resulted in some improvement two to three hours after intravenous injection of dextrose but not during the fasting state.

R. W. (case 22) had been stabilized under treatment with desoxycorticosterone acetate and sodium chloride therapy for six months before a change to the adrenal cortex extract was made. After recovery from the initial crisis, the electroencephalographic and clinical states remained static for the entire period. The patient was given 107.5 cc. of the extract in five days (table 5), without any change in the electroencephalogram in the fasting state but with definite improvement after administration of dextrose.

5. Dextrose tolerance tests were carried out by intravenous administration of 0.5 Gm. of dextrose per kilogram of body weight in 10 per cent solution over the course of thirty minutes. Determinations of blood sugar were carried out at one-half and one hour intervals, as indicated.

During treatment with desoxycorticosterone, elevation of the levels of the blood sugar to between 193 and 290 mg. per hundred cubic centimeters did not influence the electroencephalogram. This is in contrast to the effect on normal records, in which there is a definite increase in

5. The Upjohn Company, Kalamazoo, Mich., supplied the adrenal cortex extract.

TABLE 5.—*Effect on Electroencephalogram and Blood Sugars of Adrenal Cortex Extract in Cases of Addison's Disease*

Name; Sex; Age, Yr.	Case No.	Date	Treatment	Time	Stage	Percentage 8-12 per Sec. Frequency	Dominant Frequency (per Sec.)	Intravenous Dextrose Tolerance Test, Mg./100 Cc.	Comment
E. Mc. F 62	21	3/20	None	Fasting	II	19	6-8; LVF	99	Mild crisis; blood pressure 96/68; sodium 120 mEq./L.; chlorides 89 mEq./L.; hematocrit reading 48%
				½ hour	II	34	7-8	175	
		3/27	3/20-3/27: Total of 20 mg. of desoxycorticosterone acetate given intramuscularly. 3/20-3/26: 20 cc. of adrenal cortex extract q. i. d. 3/27: 20 cc. of extract given intramuscularly. 3/20-3/26: 15 Gm. sodium chloride q. i. d.	Fasting	Normal	66	8-9	100	Condition greatly improved Blood pressure 114/64; sodium 134 mEq./L.; chlorides 104 mEq./L.; hematocrit reading 32.7%
				End of infusion	Normal	81	8-9	309	
				1 hour	Normal	78	8-9	164	
				2 hours	Normal	88	8-9	127	
				3 hours	Normal	88	8-9	93	
				4 hours	Normal	71	8-9	95	
		4/7	3/27-4/7: 2-4.5 mg. of desoxycorticosterone acetate given intramuscularly q. i. d.; 5-15 Gm. sodium chloride q. i. d.	Fasting	I	37	7-8	103	Condition poorer; fever 99 to 104 F.; roentgenographic evidence of extension of pulmonary tuberculosis; blood pressure 160/100; sodium 140 mEq./L.; chlorides 111 mEq. /L.; hematocrit reading 23%
				End of infusion	I	40	7-8	228	
				1 hour	I	25	7-8	134	
				2 hours	I	28	7-8	99	
				2½ hours	I-II	26	6-8	76	
				3 hours	I	35	7-8	80	
		4/13	4/8-4/11: 10 cc. adrenal cortex extract intramuscularly q. i. d.; 4/12: 20 cc.; 4/13: 38 cc. intramuscularly and intravenously; 9 Gm. sodium chloride q. i. d.	Fasting	I	40	7-8	93	Subjective improvement; temperature 99-100.2 F.; blood pressure 136/72; sodium 132 mEq./L.; chlorides 102 mEq./L.; hematocrit reading 28%
				End of infusion	I	47	7-8	295	
				1 hour	I	50	7-8	168	
				2 hours	I	49	7-8	115	
				3 hours	I	47	7-8	85	
				3½ hours	I	48	7-8	..	
R. W. M 59	22	10/10	None	Fasting	II	19	6-7	67	Mild crisis. Blood pressure 102/70; sodium 130 mEq./L.; hematocrit reading 47%
		10/15	One intramuscular injection of 10 mg. desoxycorticosterone acetate; 5 cc. adrenal cortex extract; 60 Gm. sodium chloride	Fasting	II	5	6-7	78	Moderate crisis. Blood pressure 85/50; sodium 130 mEq./L.
				½ hour (by mouth)	II	19	6-7	91	
		10/22	Daily administration of 3 mg. desoxycorticosterone acetate intramuscularly and 9 Gm. sodium chloride orally	Fasting	II-I	36	6-8	57	Improvement. Sodium 135 mEq./L.; hematocrit reading 46 %; blood pressure 126/88
				End of infusion	II-I	32	6-8	193	
				½ hour	II-I	33	6-8	124	
				1 hour	II-I	41	6-8	81	
				1½ hour	II-I	31	6-8	63	
				2 hours	..	..	...	55	
				2½ hours	II	24	6-7	51	Hypoglycemia reaction; moderate confusion
		10/28	Daily administration of 1.5-3 mg. desoxycorticosterone acetate intramuscularly and 6-9 Gm. sodium chloride orally	Fasting	I	57	7-8	55	Sodium 137 mEq./L.; blood pressure 114/74
		12/15	1 mg. desoxycorticosterone actate intramuscularly and 5 Gm. sodium chloride orally daily; thiamine hydrochloride, 60 mg. q. i. d.	Fasting	I	58	7-9	69	Blood pressure 100/85; condition good
				End of infusion	I	48	7-8	290	
				½ hour	..	..	...	130	
				1 hour	I-II	39	6-8	73	
				2 hours	I-II	36	6-8	65	
				2½ hours	II	22	5-7	57	Hypoglycemic reaction
		1/13	1 mg. of desoxycorticosterone acetate intramuscularly and 16 Gm. sodium chloride and 300 mg. nicotinamide orally daily	Fasting	I	56	7-8	81	Blood pressure 120/80; condition good
				End of infusion	I	48	7-8	229	
				1 hour	..	..	...	116	
				1½ hours	..	..	...	94	
				2 hours	I-II	34	6-8	77	
				2½ hours	I-II	35	6-8	61	Hypoglycemic reaction
				3 hours	..	..	...	51	
				10 min. after 10 Gm. dextrose	I	51	6-8	132	
		2/20	1 mg. of desoxycorticosterone acetate intramuscularly and 25 mg. calcium pantothenate and 6 Gm. sodium chloride orally daily	Fasting	I	60	7-9	74	Blood pressure 125/75; hematocrit reading 44%; condition good
				End of infusion	I	60	7-9	257	
				½ hour	..	..	...	148	
				1 hour	..	..	...	99	
				1½ hours	..	..	...	77	
				2 hours	I-II	46	6-8	60	
				2½ hours	I-II	38	6-8	47	Hypoglycemic reaction
				3 hours	II	18	5-7	50	
				10 min. after intravenous injection of dextrose	I	55	7-8	..	

Comment.—In previous reports one of us (G. L. E.) suggested that the electroencephalographic abnormalities associated with Addison's disease were related to the disturbance in between abnormal electroencephalograms and abnormal dextrose tolerance curves and were unable to detect any improvement in the electroencephalogram after therapy with aqueous

INTRAVENOUS DEXTROSE TOLERANCE TEST IN ADDISON'S DISEASE
TREATED WITH ADRENAL CORTICAL EXTRACT
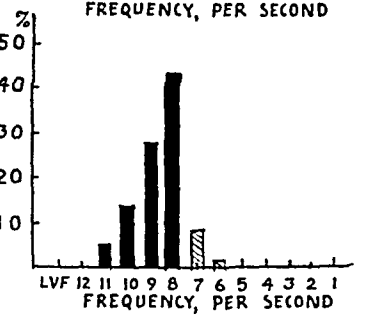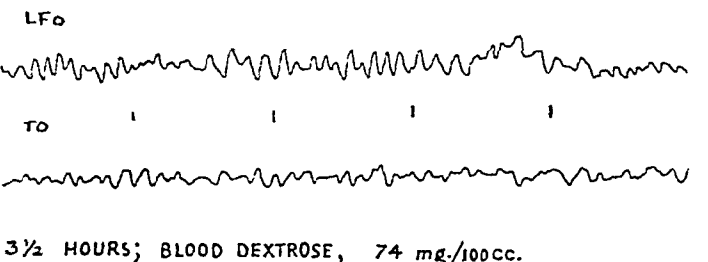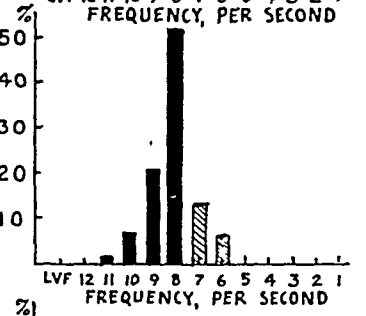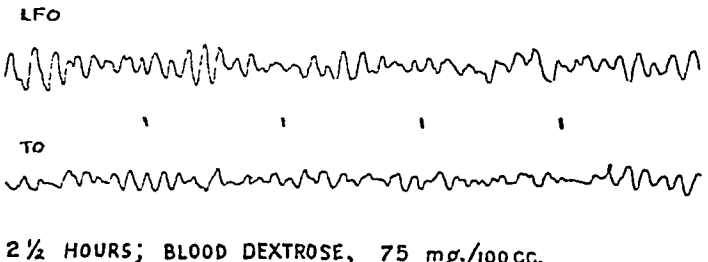
R.W. CASE NO. 22 AGE 59 4/4/42

FASTING; BLOOD DEXTROSE, 74 mg./100 cc.

END OF INFUSION; BLOOD DEXTROSE, 224 mg./100 cc.

ONE HOUR; BLOOD DEXTROSE, 128 mg./100 cc.

2½ HOURS; BLOOD DEXTROSE, 75 mg./100 cc.

3½ HOURS; BLOOD DEXTROSE, 74 mg./100 cc.
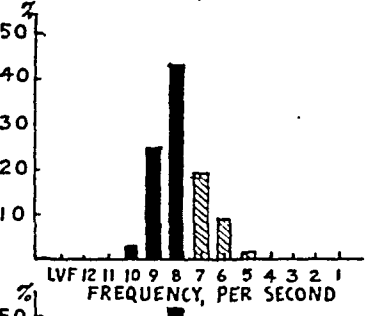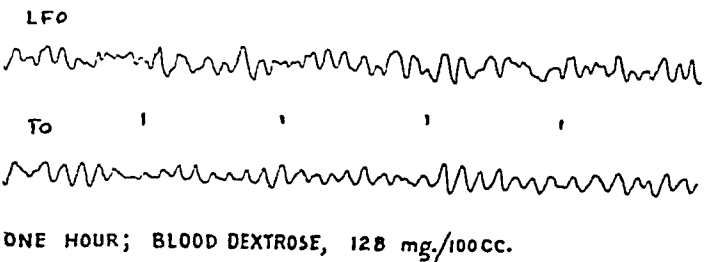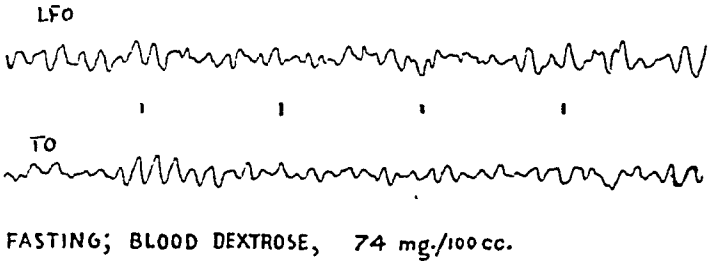
Fig. 7.—There was no improvement in the electroencephalogram with an increase in the blood sugar to 210 mg. per hundred cubic centimeters. At the end of two and a half hours the blood sugar fell to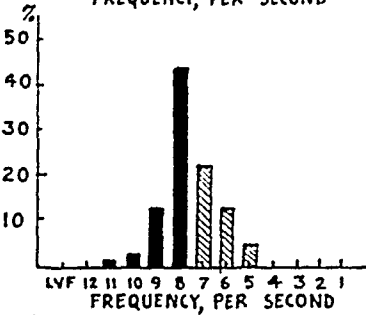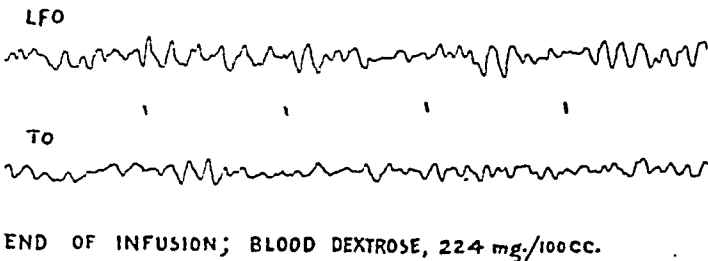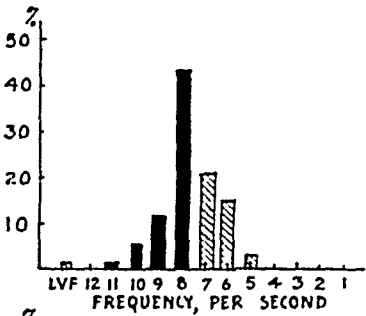 60 mg. per hundred cubic centimeters, and the patient experienced a hypoglycemic reaction, marked by confusion and sweating. The electroencephalogram became more abnormal.

carbohydrate metabolism, characteristic of Addison's disease.[4a,b] Thorn and associates,[4c] however, found no correlation with their patients adrenal cortex extract (4 to 8 cc. daily). In that study successive records were compared by gross inspection alone. The present data sug-

frequency during rising levels of the blood sugar.[6] During the period of decreasing blood sugar, however, the electroencephalogram showed slower and more abnormal activity.

R. W. (case 22) invariably displayed a hypoglycemic reaction with obvious confusion two and one-half hours

normal at this point but promptly improved when more dextrose was administered (fig. 7).

During treatment with adrenal cortex extract, the dextrose tolerance curves were higher, hypoglycemic reactions did not occur and the electroencephalogram either was unchanged or improved progressively during the period of falling levels of the blood sugar, in contrast to the results during treatment with desoxycorti-
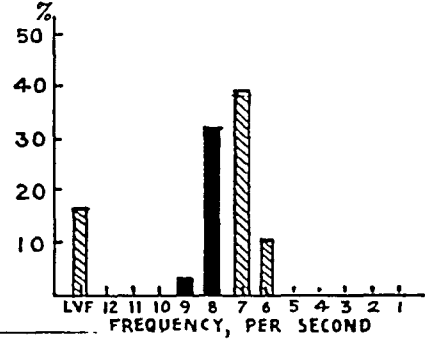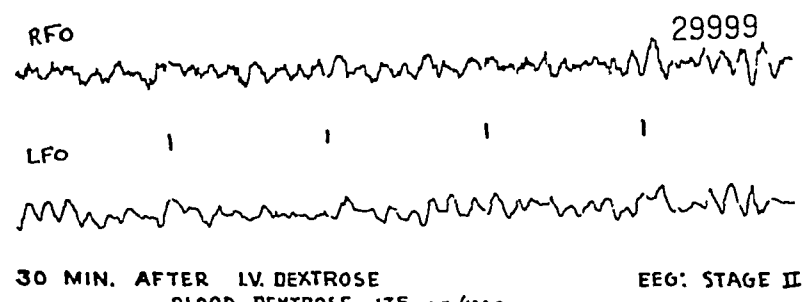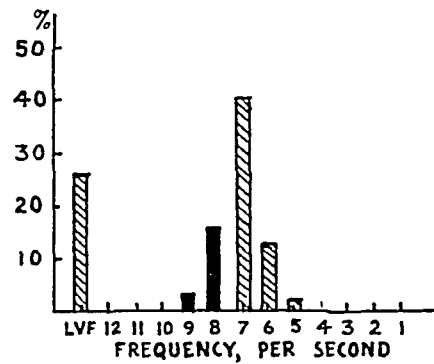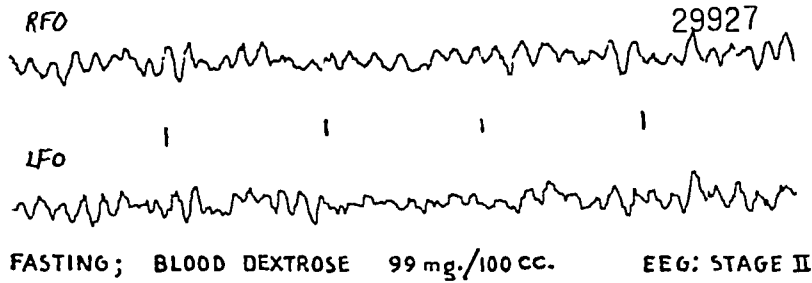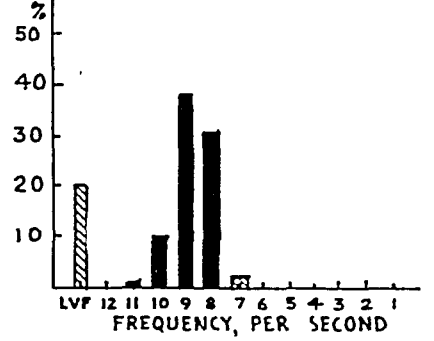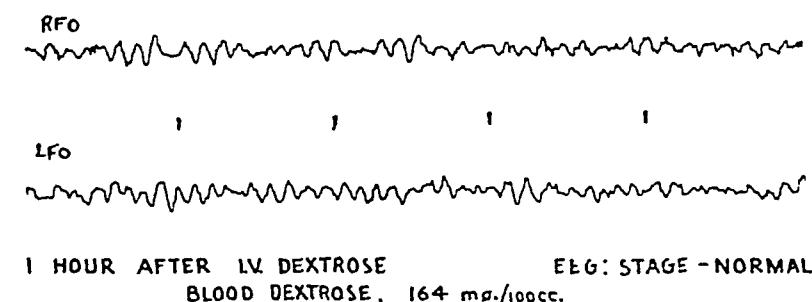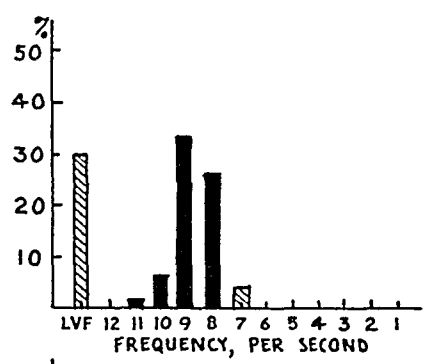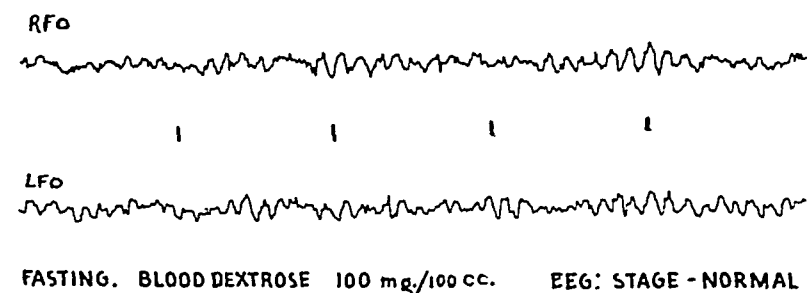
Fig. 6.—The electroencephalogram shifted from stage II to a normal pattern after one week of therapy with adrenal cortex extract, desoxycorticosterone acetate and sodium chloride. The mental status improved correspondingly.

after completion of the infusion (with the blood sugar at a level of from 47 to 61 mg. per hundred cubic centimeters). The electroencephalogram was most ab-

costerone. The maximum improvement occurred three to three and one-half hours after the infusion of dextrose, or four to six hours after the last injection of extract, the time of maximum action (fig. 8).

6. Engel, G. L.; Romano, J.; Ferris, E. B., Jr.; Webb, J. P., and Stevens, C. D.: A Simple Method of Determining Frequency Spectrums in the Electroencephalogram: Observations on Effects of Physiologic Variations in Dextrose, Oxygen, Posture and Acid-Base Balance on the Normal Electroencephalogram, Arch. Neurol. & Psychiat. 51:134 (Feb.) 1944.

costerone, which has no effect on carbohydrate metabolism, alone or with dextrose, was ineffective. This, again, suggests, but does not prove, that at least in part the electrical abnormalities of the brain associated with Addison's disease are directly or indirectly related to disturbances in carbohydrate metabolism. The question of the relation of certain sterols of the adrenal cortex to carbohydrate metabolism of the brain warrants further study.

COMMENT

The data presented in this report further confirm the dynamic character of the electrical changes occurring during delirium.[1] In many instances the effects produced by the methods described yielded an accurate preview of the changes that occurred spontaneously days or weeks later, during recovery from the primary disease process. The response, when it occurred, followed essentially the same pattern of progressive stages as that which was noted spontaneously, but it was independent of the nature of the provoking factors.

Little can be said at this time about either the mechanism or the specificity of these responses. The choice of clinical material in the various experimental categories was based on well established clinical practices. We do not know as yet, for example, whether administration of oxygen would be effective with conditions other than cardiac and pulmonary decompensation. The fact that all but 1 of the patients with cardiac decompensation had normal oxygen saturation of arterial blood and yet many responded well to administration of oxygen makes it clear that simple anoxemia is not the sole determining factor. Recent studies on normal subjects [6] have demonstrated a shift in alpha frequency during the administration of 100 per cent oxygen. Similarly, while we have demonstrated a return toward the normal response to administration of dextrose in patients with Addison's disease treated with aqueous adrenal cortex extract in contrast to the desoxycorticosterone is given, the effects of dextrose in patients with delirium from other causes have not yet been investigated. Further studies, including measurements of the total cerebral oxygen uptake, are contemplated in an attempt to clarify some of these problems.

Regardless of the mechanisms, however, it is clear from these data that the intelligent treatment of delirium must include efforts to reverse the major physiologic derangements accompanying the underlying disease. The statement that permanent cortical damage becomes increasingly

likely the longer the noxious factors are active is amply supported by clinical and electroencephalographic observation. The greatest range of reversibility is found in the early and acute phases. The delirious cardiac patient with pulmonary disease should not be permitted to remain anoxemic until spontaneous recovery occurs. Cheyne-Stokes respiration should be terminated by any available method, such as administration of oxygen or theophylline ethylenediamine. Special attention should be directed toward restoration of the normal physiologic and biochemical milieu of the brain and avoidance of the addition of further noxious factors, e. g., certain drugs.

SUMMARY

One hundred per cent oxygen was administered in a total of 20 experiments to 9 delirious patients with congestive heart failure and to 4 delirious patients with pulmonary decompensation. The electroencephalogram showed definite improvement in 10 experiments, probable improvement in 7 experiments and no significant change in 3 experiments.

Three patients with congestive heart failure showed more abnormalities in the electroencephalogram when they were in the recumbent than when they were in the sitting position.

Four of 6 patients with Cheyne-Stokes respiration showed phasic variations in the electroencephalogram corresponding to the phases of respiration. The electroencephalogram improved during the hyperpneic phase and showed more abnormalities during the apneic phase. For 2 patients with pronounced stage IV electroencephalograms no significant changes were demonstrable.

One patient with extreme anemia of unknown cause had a more normal electroencephalogram after blood transfusion. The hemoglobin concentration rose from 2.5 to 5.8 Gm. per hundred cubic centimeters.

Two patients with Addison's disease were studied during therapy with desoxycorticosterone acetate and adrenal cortex extract. Adequate treatment with the former resulted in improvement in the electroencephalogram, but not in complete restoration to normal. Large amounts of adrenal cortical extract, sufficient to produce a significant change in the dextrose tolerance curve, resulted in further improvement in the electroencephalogram, particularly during administration of dextrose.

In the treatment of delirium correction of reversible physiologic disturbances is important

Cincinnati General Hospital.

gest that a number of factors are involved. During the crisis disturbances in the level of awareness are common and are associated with electroencephalographic changes. However, with electroencephalogram improves but does not necessarily become normal. Complete, or almost complete, return to normal of the electroencephalogram was attained only when a large amount

INTRAVENOUS DEXTROSE TOLERANCE TEST IN ADDISON'S DISEASE
TREATED WITH DESOXYCORTICOSTERONE

R.W. CASE NO. 22   AGE 59   3/31/42
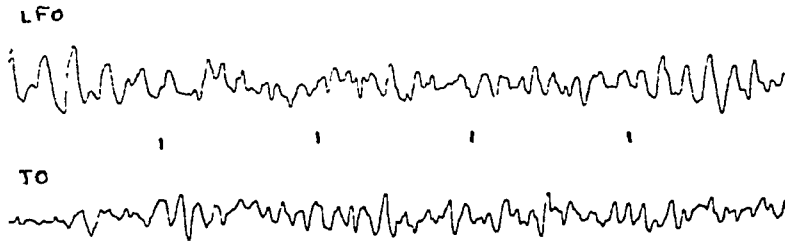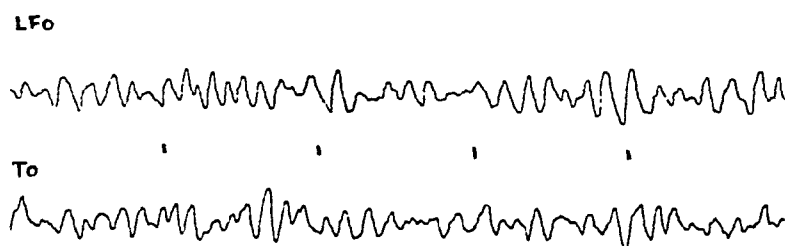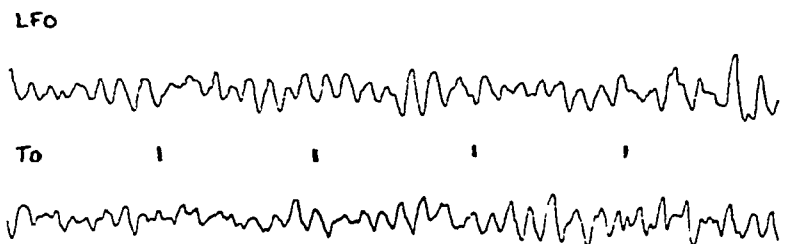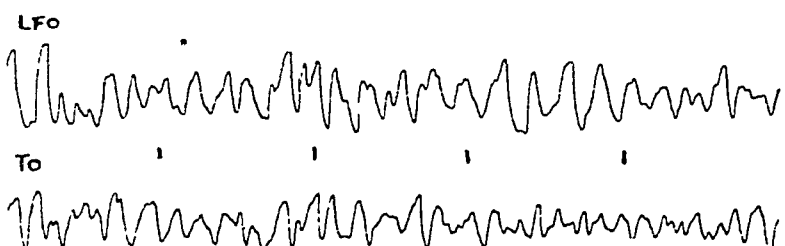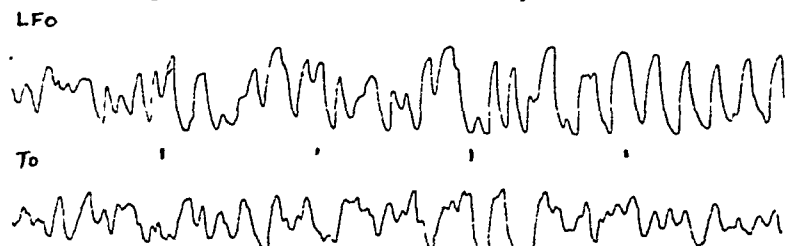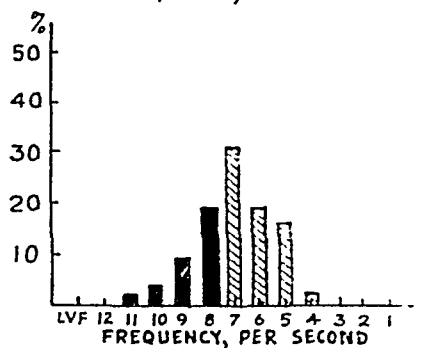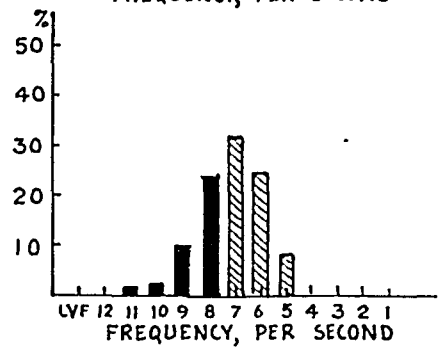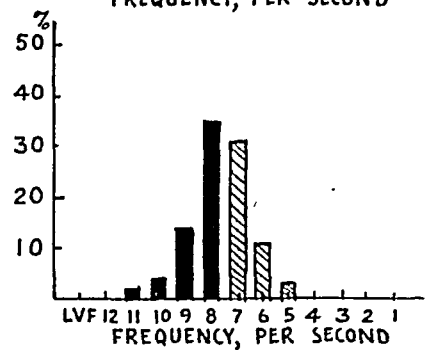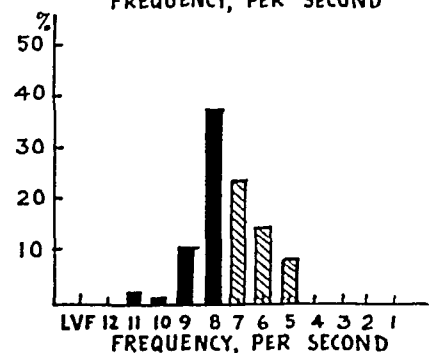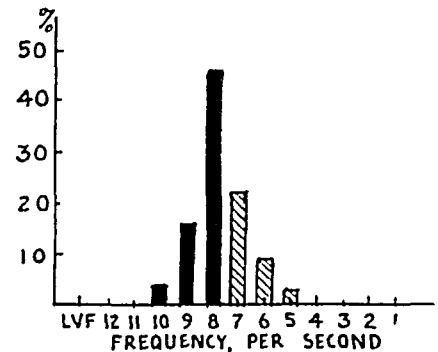
Fig. 8.—Electroencephalograms for the patient whose record appears in figure 7, after treatment with the extract for five days. There was no hypoglycemic reaction, and the electroencephalogram improved progressively in spite of falling levels of the blood sugar.

clinical and chemical recovery from crisis, the mental status returns to normal, while the of aqueous adrenal cortex extract or the extract plus dextrose was administered. Desoxycorti-

picture of the effect of a mild acidifying agent. The p_H was lowered to from 5 or 6, and the excretion of ammonia, fixed base and titrable acid was increased. In 3 of 4 patients a definite, but temporary, diuretic effect of the amino acid hydrochloride was evident.

From the seventy-two hour specimen of urine of 3 of the patients, the isolation of d (—)-glutamic acid was undertaken. Since, according to Ratner,[5] the unnatural isomer of glutamic acid is excreted in rats as pyrrolidincarboxylic acid, the urines were brought to a concentration of twice normal hydrochloric acid and hydrolyzed for sixteen hours on the steam bath. Customarily the isolation of glutamic acid from urine is carried out by means of the Neuberg precipitation method, with successive precipitations of the barium or the calcium salt. In order to save the mercury salt, the first step was eliminated and

The following 2 cases are illustrative of the results obtained in treatment of classic petit mal epilepsy.

CASE 1.—Repeated neurologic and physical examinations of the patient, a 12 year old boy, revealed nothing abnormal. Petit mal seizures, which had occurred at a frequency of from twenty-five to fifty or more a day for four years, were unaffected by diphenylhydantoin sodium–phenobarbital therapy. A six months' trial with the ketogenic diet resulted in moderate reduction in the number of seizures, but the patient refused to continue under the rigid regimen. Administration of dl-glutamic acid hydrochloride, in daily doses of 12 Gm., resulted in reduction in the number of seizures to from five to twenty-five a day. The parents, school instructors and friends reported spontaneously that the patient was more congenial, cooperative and affable. Peculiar egocentric attitudes were decreased. Concentration and application in his school work were improved.

The seizures recurred at their former frequency after the administration of dl-glutamic acid hydrochloride was discontinued. Use of ammonium chloride, 4 Gm. a day, failed to alter the frequency or character of the seizures.

Acid-Base Balance of Blood and Urine of Patient R. J.

Date, 1943	Hematocrit Reading	Carbon Dioxide, mEq. per Liter	Serum Chloride, mEq. per Liter	Volume, Liters	p_H	Urine (24 Hours)			Comment
						Titrable Acid, mEq.	Ammonia, m.Eq	Total Base, mEq.	
1/12	48	28.9	96	2.7	7.0	13.5	25.0	535	
1/26	..	31.3	97	2.6	6.6	23.7	19.0	418	
2/10	44	32.1	100	1.6	6.3	28.2	42.0	342	
2/23	50	32.8	95	2.0	5.8	35.4	83.0	430	12 Gm. dl-glutamic acid
3/ 9	..	30.5	96	4.0	5.8	52.0	110.0	580	hydrochloride
3/23	44	29.2	97	3.4	5.0	69.0	134.0	640	
4/ 6	44	30.0	100	2.4	5.7	36.0	84.0	450	
4/20	..	....	...	2.8	5.6	44.0	81.0	360	
5/11	42	28.6	97	2.0	6.4	22.0	71.0	572	16 Gm. dl-glutamic acid
6/ 8	46	31.0	95	2.6	6.0	33.0	73.0	456	hydrochloride
7/22	42	29.4	102	1.0	5.3	52.0	76.0	...	

the glutamic acid precipitated directly from the hydrolyzed and concentrated urine by addition of barium hydroxide and 5 volumes of alcohol.

From each of the urines the unnatural, d (—), glutamic acid was isolated in pure form in small yield. On the basis of the daily intake of the racemic acid, 20 per cent of the unnatural isomer was isolated from the urine of patient S. K., 15 per cent from the urine of patient M. B. S. and 7 per cent from the urine of patient J. R.

EFFECT OF ADMINISTRATION OF l (+)-GLUTAMIC ACID

When l (+)-glutamic acid was administered to about 20 patients who had experienced recurrent petit mal seizures, both the frequency and the severity of the attacks were reduced. Attacks of grand mal were essentially unchanged or were increased in frequency. The effect on psychomotor seizures was less easy to demonstrate but was often commented on by the patient and his relatives.

Carbaminoylcholine chloride, 26 mg. in divided doses, combined with diphenylhydantoin sodium, 0.3 Gm., failed to reduce materially the frequency of the attacks. The number of days during which only twenty-five attacks occurred increased, with a relative decrease in the number of days on which fifty attacks were noted.

Carbaminoylcholine-diphenylhydantoin therapy was replaced by administration of l (+)-glutamic acid. A larger quantity than 8 to 12 Gm. was not required to obtain a favorable result. A further reduction of the frequency of the attacks over that observed with dl-glutamic acid hydrochloride was noted. The patient's parents and school instructors reported that there were days during which no seizures were observed, and the patient stated that he was not aware of momentary interruptions of consciousness on these days.

Improvement in personality was similar to, and qualitatively identical with, the changes noted during administration of dl-glutamic acid hydrochloride.

In this case, there is little doubt that the improvement, both in the frequency of seizures and in emotional stability, was related to administration of l (+)-glutamic acid alone. Diphenylhydantoin sodium, diphenylhydantoin-phenobarbital therapy, a ketogenic diet, ammonium chloride and carbaminoylcholine-diphenylhydantoin ther-

5. Ratner, S.: J. Biol. Chem. 152:559, 1944.

BIOCHEMICAL ASPECTS OF GLUTAMIC ACID THERAPY FOR EPILEPSY

HEINRICH WAELSCH, M.D., Ph.D., and J. C. PRICE, M.D.

NEW YORK

Recently, the use of *dl*-glutamic acid hydrochloride in the treatment of epileptic patients suffering from seizures of the petit mal and the psychomotor type was described.[1] Administration of the racemic amino acid hydrochloride to patients who were resistant to the usual anticonvulsant therapy resulted in a decrease in the frequency of seizures and in an increase in mental and physical alertness. The anticonvulsant therapy, though ineffective previously, was continued through the period of administration of the amino acid hydrochloride. Seizures of the grand mal type were unaffected, or were increased, by this treatment.

It is of primary interest to discover the mechanism through which *dl*-glutamic acid hydrochloride exercises its effect, and the experiments described in this paper were directed toward this objective.

As was pointed out previously,[1] the use of the *dl*-glutamic acid hydrochloride was suggested (*a*) by the close relation of the natural, *l* (+) isomer to cerebral metabolism and (*b*) by the mildly acidifying effect which the racemic amino acid hydrochloride would be expected to have. Studies on the influence of the administration of *dl*-glutamic acid hydrochloride on the acid-base balance of the blood and urine and the fate of this substance in the human subject and on the effect of administration of the *l* (+) isomer indicate that the therapeutic results may be ascribed in large part to the *l* (+)-glutamic acid, and not to the acidifying effect of the racemic amino acid hydrochloride.

EXPERIMENTAL DETERMINATION OF ACID-BASE BALANCE

The subjects of the investigation were patients with seizures of the petit mal or psychomotor type. The beneficial effect of the administration of *dl*-glutamic acid hydrochloride on 3 of the patients (S. K., R. J. and M. B. S.) was described previously.[1] It was impossible to hospitalize the patients throughout the investigation, but at approximately three week intervals they stayed in the hospital for a three day period, during which samples of the blood and urine were collected under controlled conditions. On the morning of the third day a sample of blood was withdrawn before breakfast, and the cell volume, the carbon dioxide content and the chloride concentration of the serum were determined by standard laboratory procedures.[2] The urine of the twenty-four hours preceding the taking of the sample of blood was collected under toluene, and the p_H (glass electrode method) and the values for ammonia, titrable acid,[2] and total base[3] were determined. The first three sets of data, obtained during the first six weeks, served as controls. On the day following the third collection of blood and urine, the administration of *dl*-glutamic acid hydrochloride was begun.

Since the results were similar for all the patients studied, the data for only 1 of them are given in the accompanying table. The carbon dioxide content and the chloride concentration of the serum during the administration of the racemic amino acid hydrochloride did not vary significantly from the control values, which were found to agree in magnitude and variation with those for healthy human subjects, as determined by Shock and Hastings.[4] Of the patients who received daily 2.4 to 3.6 Gm. of hydrochloric acid as glutamic acid hydrochloride, the chloride concentration in the serum of only 1 (M. S. B.) appeared to have increased slightly (from 102 to 108 millimols). No significant shift occurred in the acid-base balance even after prolonged intake of glutamic acid hydrochloride.

Since the sample of blood was taken at least fourteen hours after the last intake of *dl*-glutamic acid hydrochloride, these conclusions apply only to permanent changes in the acid-base balance of the blood. No study of the immediate effect of the intake of the *dl*-amino acid hydrochloride was undertaken.

The urine of the patients after administration of *dl*-glutamic acid hydrochloride presented the

1. Price, J. C.; Waelsch, H., and Putnam, T. J.: *dl*-Glutamic Acid Hydrochloride in Treatment of Petit Mal and Psychomotor Seizures, J. A. M. A. **122**:1153 (Aug. 21) 1943.

2. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1932.

3. Consolazio, W. V., and Talbott, J. H.: J. Biol. Chem. **132**:753, 1940.

4. Shock, N. W., and Hastings, A. B.: J. Biol. Chem. **104**:585, 1934.

Furthermore, the substance may act indirectly by influencing organs other than the nervous tissue or by modifying the absorptive process in the intestine of substances, such as minerals.[6]

In consequence of the results obtained with glutamic acid in treatment of patients with petit mal, two studies were carried out which may have a bearing on the understanding of the mechanism involved. Zimmerman and Ross [7] investigated the effect of l (+)-glutamic acid and dl-pyrrolidincarboxylic acid on the maze-learning ability of rats, as measured by the number of trials and errors and the time required by the animals to run the maze. Rats which received glutamic acid or its derivative showed significantly greater learning ability than the controls, which were fed the complete balanced diet without the amino acid supplement. The addition of aminoacetic acid to the diet had no effect. The results of these experiments, which were suggested by observations on the mental behavior of patients receiving glutamic acid, give further indication that glutamic acid appears to influence cortical activity by direct or indirect means. Furthermore, the comparison with aminoacetic acid shows that this is not a property peculiar to all amino acids.

Recently, Nachmansohn, John and Waelsch [8] showed that glutamic acid has an adjuvant action on the enzyme system which synthesizes acetylcholine from choline and acetic acid.[9] After the enzyme extract was dialyzed, the decreased synthesizing power of the system could be restored partially by addition of glutamic acid (or citric acid) to the extract. These observations, which point to specific involvement of glutamic acid in biochemical mechanisms intimately connected with the function of nervous tissue, may become of increased importance if there should be found a deficiency of glutamic acid or substances metabolically related to it in patients with petit mal.[10]

At this point in the study it is not possible to obtain a common denominator for the effect observed with glutamic acid and that observed with other substances used in treatment of patients subject to attacks of petit mal. The outstanding therapeutic measure, namely, the ketogenic diet, produces not only an increased concentration of ketone bodies, but acidosis. The doubtful results obtained with ammonium chloride and the probable exclusion of an acidotic effect of glutamic acid therapy suggest the possibility that the acidosis accompanying the use of the ketogenic diet may not be directly responsible for the effects observed. It is possible that the production of acetoacetic acid influences the acetylation of choline to acetylcholine.

It is of major interest in this connection that glutamic acid is effective only in treatment of patients with petit mal. In patients suffering from attacks of grand mal glutamic acid not only is ineffective but sometimes actually increases the number of such seizures. This observation is a further indication of the differences in the various types of epilepsy, as has already been shown by the difference in brain wave patterns and by the preferential effectiveness of diphenylhydantoin sodium in cases of grand mal and of the ketogenic diet in cases of petit mal. It is interesting that experimentally increased concentrations of acetylcholine can produce generalized seizures.[11] In contrast to this, other experiments point to the possibility that there may be a deficiency in the synthesis of acetylcholine in patients with petit mal. A final decision as to the mechanism involved in the action of glutamic acid, however, must be left to future experiments.

SUMMARY

The administration of dl-glutamic acid hydrochloride in amounts which benefit patients suffering from attacks of petit mal does not result in a significant shift of the acid-base balance of the blood. Urinalysis showed the effect of a mildly acidifying agent; d (—)-glutamic acid was isolated from the urine of the patients.

Administration of l (+)-glutamic acid is as effective as that of dl-glutamic acid hydrochloride. These results suggest that the therapeutic effects may be ascribed to the l (+)-glutamic acid.

6. McCance, R. A.; Widdowson, E. M., and Lehmann, H.: Biochem. J. **36**:686, 1942.

7. Zimmerman, F. T., and Ross, S.: To be published.

8. Nachmansohn, D.; John, H. M., and Waelsch, H.: J. Biol. Chem. **150**:485, 1943.

9. Nachmansohn, D., and Machado, A. L.: J. Neurophysiol. **6**:397, 1943.

10. Krebs (Biochem. J. **29**:1951, 1935) found that brain tissue contains an enzyme which synthesizes glutamine from l (+)-glutamic acid and NH_4^+, a reaction which is inhibited by the presence of the unnatural isomer of glutamic acid. It has been reported recently (Sapirstein, M. R.: Proc. Soc. Exper. Biol. & Med. **52**:334, 1943) that generalized seizures in rabbits produced by intravenous administration of an ammonium salt may be suppressed by a preceding intravenous injection of l (+)-glutamic acid.

11. Brenner, C., and Merritt, H. H.: Effect of Certain Choline Derivatives on Electrical Activity of Cortex, Arch. Neurol. & Psychiat. **48**:382 (Sept.) 1942.

apy had neither reduced the frequency of attacks nor improved the personality of the patient.

CASE 2.—A man aged 23 was in good health until ten years ago, when he became aware of short lapses of consciousness. His parents and friends recalled periods during which he failed to answer questions, ceased talking and apparently stared into space. The attacks recurred at the rate of five to fifty per day.

The first of a series of eight grand mal attacks occurred six years ago. Repeated physical and neuro logic examinations revealed nothing significant. A roentgenogram of the skull, a pneumoencephalogram, a complete blood count, the results of urinalysis and the basal metabolic rate were normal. Values for the blood sugar had been noted by previous observers to range from 46 to 98 mg. per hundred cubic centimeters, both in the fasting state and as single estimations obtained during a dextrose tolerance test. Dextrose, dextrose-insulin and insulin tolerance curves were within normal limits.

Phenobarbital, diphenylhydantoin sodium and bromides, either alone or in combination, were ineffective in reducing the attacks. The ketogenic diet was poorly tolerated by the patient. Ammonium chloride failed to ameliorate the symptoms.
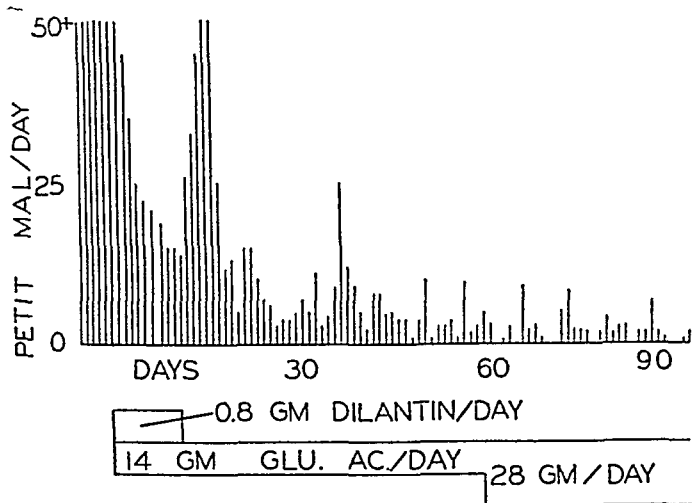
Effect of administration of $l(+)$-glutamic acid in varying doses, with and without diphenylhydantoin sodium, on the frequency of petit mal seizures.

The attacks were notably reduced during a fasting period of thirty-six hours. They increased during administration of a diet containing 300 Gm. of carbohydrate daily. Administration of diphenylhydantoin sodium (0.4 Gm.) was continued throughout the tests, as in the control period.

Administration of l-glutamic acid in doses of 14 to 28 Gm. daily, with or without diphenylhydantoin sodium, was associated with a reduction in the frequency of attacks which was roughly proportional to the dose. The occurrence of seizures varied from none up to ten daily, and their severity was decreased. In this case, l (+)-glutamic acid was decidedly more effective than the other measures tried. The morale of the patient was improved; however, there was no evidence of any effect on the personality or the emotional stability. The p_H of the urine (glass electrode method) fluctuated within a range of 6 to 7.5, with occasional lowering to 5.5.

COMMENT

In the beginning of our study, dl-glutamic acid hydrochloride and l (+)-glutamic acid were given only in combination with anticonvulsant drugs, despite the fact that the drug therapy had

proved ineffective for the patients concerned. Later, the glutamic acid preparations were given patients without an accompanying drug, as in the 2 cases described in this paper. The results presented here indicate that the effect observed was due to the administration of the natural, l (+) isomer. No shift in the acid-base balance of the blood following the administration of dl-glutamic acid hydrochloride could be detected with the methods applied, and the decrease in seizures occurred too soon for it to appear likely that this was the effect of a mildly acidifying agent. The administration of the acidifying substance expressed itself in lowering of the p_H of the urine, in an increased excretion of ammonia and in a slight increase of the excretion of total base and of titrable acidity.

Whereas the lack of an acidifying effect on the blood of the racemic acid hydrochloride does not exclude the possibility that some other property of the racemate might be responsible for the therapeutic effect observed, the clinical observations after the administration of the l (+) isomer make it probable that this compound is the effective component of dl-glutamic acid hydrochloride. The fact that a naturally occurring, nonessential amino acid, which is a major component of the food and body proteins, has a distinct action, otherwise encountered only with essential food components, is of particular biochemical interest. A daily protein intake of 70 Gm. would correspond approximately to an intake of natural glutamic acid of 7 to 10 Gm. The proteins of the body itself contain between 10 and 20 per cent of glutamic acid. It is remarkable, therefore, that as little as 4.8 Gm. of l (+)-glutamic acid administered in 12 Gm. of the racemic hydrochloride should have the therapeutic effect observed. Furthermore, glutamic acid occupies a central position in the metabolic processes involving transamination and carbohydrate cycles, a fact indicating the rapid metabolic transformation this amino acid undergoes in the body.

From our results, it appears that in spite of the abundant occurrence of a particular compound in the food and body and the ease with which it can be synthesized in the body, relatively small amounts of it, administered in addition to a balanced diet, may have beneficial effects under certain conditions. It is indubitably too early to interpret our results in terms of a possible deficiency which is overcome by the administration of glutamic acid. Nothing is known about the specificity of the observed action. There might well be other nitrogenous, or nonnitrogenous, body constituents which have the same effect as that observed with glutamic acid.

ideas of sinfulness multiplied, and self condemnation became more persistent. At times she moaned all day and was either very restless or mute and motionless. Physical examination revealed nothing significant. The diagnosis of involutional melancholia was established.

Two months after her admission her condition became somewhat worse. After a wet pack her temperature rose to 106.4 F., but she had no physical complaints. Rales were discovered at the base of the right lung, and, although a roentgenogram of the chest revealed nothing significant, a diagnosis of bronchopneumonia was made. The temperature rapidly returned to normal. During November 1941, for the first time, her symptoms became less severe. She was then transferred to a ward for the chronically ill, where she had several exacerbations of the psychosis; she admitted having auditory hallucinations of a derogatory nature and made several suicidal attempts.

Electric Shock Treatment.—On July 6, 1942 electric shock therapy was begun. She was given three treatments a week and by August 5 had had one petit mal and thirteen grand mal convulsions. The dose ranged from 110 to 140 volts, applied for two-tenths second. The convulsion and the postconvulsive state were of the usual character. After a few treatments she showed signs of improvement, which progressed until finally she was free of delusions and hallucinatory experiences. She was no longer depressed and self condemnatory and took an interest in herself and her surroundings. Treatment was finally stopped because she became slightly elated and confused after the twelfth treatment. Although she was informed that she would be released after a short rest, she kept insisting that she be sent home immediately because she felt well and wanted to attend her niece's wedding. She became moderately restless, but transfer to a ward for disturbed patients was not necessary until 1 a. m. of August 11. At this time she became acutely disturbed, screamed and assaulted people about her. It was necessary to place her in restraint, and during that day she received ¼ grain (15 mg.) of morphine sulfate and ¹⁄₁₀₀ grain (0.6 mg.) of scopolamine hydrobromide at 10 a. m., 2 p. m. and 9 p. m. However, she slept little and struggled against her restraints most of the time. She refused to eat and had to be fed with a tube. At 7:30 a. m. of August 12 her temperature was 108 F. plus; her skin was dry, and her tongue was parched. She was extremely restless, kept screaming unintelligible words and seemed to be using her last ounce of energy. At this time she received 1.5 cc. of a 25 per cent solution of nikethamide (pyridine betacarboxylic acid diethylamide) intramuscularly and 50 cc. of a 50 per cent solution of dextrose intravenously. She was packed in ice, and administration of 5 per cent dextrose isotonic solution of sodium chloride by clysis was begun. At 8:30 a. m. 5 grains (0.3 Gm.) of barbital sodium and 3.5 grains (0.2 Gm.) of sodium amytal were administered intramuscularly, in an attempt to quiet her. Her temperature fell to 104.4 F. by 9:15 a. m. but rose to 106.4 F. one hour later. By this time she exhibited convulsive movements involving her whole body and sometimes resembling status epilepticus. She was, therefore, given 3 grains (0.19 Gm.) of sodium amytal intravenously. This stopped the convulsive movements. However, her pulse soon became so weak and her general depression so profound that it was feared she was about to die. The corneal reflexes were absent and the pupillary reflexes poor. She was then given 1 cc. of epinephrine hydrochloride (1:1,000) intramuscularly and 1.5 cc. of a 25 per cent solution of nikethamide intracardially. Her

pulse could not be obtained, but she continued to breathe regularly and rapidly. All this time she was absorbing the hypodermoclysis well. At 11 a. m. her temperature was 100.2 F., and the ice was removed from her body. She became a little restless and moaned unintelligibly, but could not speak. At 12:50 p. m. she was given 1.5 cc. of a 25 per cent solution of nikethamide because her pulse was imperceptible. She responded to the pain of the injection by thrashing about. At 2 p. m. her temperature was 100 F. At 3:10 p. m. another 1.5 cc. of the solution of nikethamide was given intramuscularly to maintain her cardiovascular system. At 3:30 p. m. it was noted that she was absorbing the clysis rather poorly, and at 4 p. m. her temperature was up to 102 F. Her lungs were clear except for occasional moist rales. Her temperature slowly rose; respirations became more shallow and rapid, and her pulse became imperceptible. At 7 p. m. her temperature was 106.2 F. and her respirations 52 a minute. She died at 7:30 p. m.

CASE 2.—*Family and Past History.*—D. M., a Negro, was born in North Carolina in May 1908 and completed the seventh grade of elementary school. During childhood he had no unusual illnesses. As a rule he was moderate in his habits but periodically drank whisky heavily. In June 1939 signs of early syphilis developed, for which he was treated by the intravenous injection of 1 Gm. of mapharsen within a five day period. He had no complications, and during the period of observation the serologic reactions of the blood remained positive. In October 1939 a generalized papular eruption developed, and he again was given intravenous injections by the drip method, 1.2 Gm. of mapharsen being administered within five days. No complications arose, and he was treated and observed further at the New York Hospital Clinic. The serologic reaction became negative in January 1940. In September 1942 the clinic reported that physically he showed no evidence of syphilis. The Wassermann reaction of the blood was negative, and that of the spinal fluid was also negative except for a 2 plus reaction in the last two tubes. Previously the reaction had been negative throughout. This change in the reaction of the spinal fluid was thought to be an artefact. The patient was described as good natured, friendly and sociable. The family history was stated to be negative for nervous and mental disease.

Psychosis.—Little exact information could be obtained from the patient's associates, but it was thought that he had become mentally ill about one month before his admission to the state hospital, on Nov. 25, 1942. He caused a disturbance at his home, but had not been drinking. At the hospital he expressed grandiose and persecutory delusions and admitted having auditory hallucinations of a religious character. He cooperated well and was correctly oriented in all spheres. The first physical examination made on admission disclosed some slurring of test phrases and perioral tremor. However, the pupils were round and regular and reacted well to light and in accommodation, and the deep reflexes were active and equal on the two sides. Physical examination otherwise revealed nothing significant. His blood pressure was 104 systolic and 62 diastolic. On Dec. 9, 1942 the Wassermann reactions of the blood and spinal fluid were reported to be completely negative. At this time he showed no perioral tremor, but his speech was a little slurred. He showed no sensorial defects, but was manneristic and at times silly. The diagnosis was dementia precox, paranoid type.

FATALITIES ASSOCIATED WITH ELECTRIC SHOCK TREATMENT OF PSYCHOSES

REPORT OF TWO CASES, WITH AUTOPSY OBSERVATIONS IN ONE OF THEM

ALEXANDER GRALNICK, M.D.

CENTRAL ISLIP, N. Y.

A small number of deaths due to electric shock have been reported in the literature since the introduction of electrotherapy. Kolb and Vogel [1] estimated a death rate of 0.05 per cent in 7,207 cases, and Impastato and Almansi,[2] a mortality rate of 0.8 per cent in 11,000 cases. As a rule, death is due to a defect in some organ other than the brain—usually the heart—which is aggravated by the convulsive treatment. However, some deaths are completely unexplainable. Impastato and Almansi,[2] Ziegler [3] and Ebaugh and his associates [4] reported cases in which failure of the heart played the deciding role. Cash and Hoekstra [5] and Ebaugh and associates [4] recorded fatalities in cases in which curare was given before the electric convulsion. Cash and Hoekstra [5] stated that death came suddenly, about two hours after the treatment, and was probably of cardiac origin. Ebaugh and associates [4] stated that immediate pulmonary arrest caused death.

Ebaugh and associates [4] tabulated in some detail the data in 9 cases which had been reported in the literature up to July 1942. The ages in 7 of these cases ranged from 50 to 79; in 1 case the patient was 45 and in 1 29 years of age. In 3 cases death occurred one to four months after the treatment, and in the other 6 cases, anywhere from immediately to three days after a treatment. The latter cases are the significant ones because the time of death followed so closely the induced convulsion. In 4 of these 6 cases death followed the treatment immediately and was due to cardiac or respiratory failure; in 1 case coronary thrombosis caused the patient's death one hour and thirty-five minutes after the treatment, and in 1 case the patient died in status epilepticus three days after the treatment. In 4 of these 6 cases, again, one to three treatments were given; in 1 case, nineteen treatments, and in 1 case, thirteen treatments. In 3 cases autopsy was performed; in 1 of these the patient, aged 75, had advanced changes associated with arteriosclerosis, and the brains in the other 2 cases, in each of which the patient was 57 years of age, showed several small areas of cortical devastation, diffuse degeneration of nerve cells in the cortex, small areas of recent necrosis and astrocytic proliferation. These last 2 cases were reported by Ebaugh and his co-workers.

The following 2 cases are reported here for their interest and because they add material for future study in a still obscure field.

REPORT OF CASES

CASE 1.—*Family and Past History.*—M. B. was born Nov. 15, 1898. She had no unusual diseases in childhood and graduated from grammar school at the age of 14. She worked regularly from this time except for a few weeks in her twenty-eighth year, when she was confined to a convalescent home because she was "run down from overwork." She married at the age of 37 and had an abortion one year later. She was of Protestant faith, went to church regularly and was moderate in her habits. She was described as worrisome and conscientious in her work. The family history was negative for nervous and mental disease.

Psychosis.—The first change in her behavior was noted in the early part of February 1941, when she showed an abnormal interest in Christian Science Shortly thereafter, she began to think that she had cancer and went to several physicians, who could not dissuade her from the idea. She became depressed and self condemnatory and expressed the opinion that her mind was "slipping." She continued to work, nevertheless, until one week before her admission to the hospital, on July 3, 1941. She finally became so agitated that the family could not manage her, and the physician advised hospitalization.

On admission there was accentuation of her leading symptoms. The agitation and depression increased;

1. Kolb, L., and Vogel, V.: The Use of Shock Therapy in Three Hundred and Five Mental Hospitals, Am. J. Psychiat. **99**:90-100 (July) 1942.

2. Impastato, D., and Almansi, R.: A Study of Over Two Thousand Cases of Electrofit-Treated Patients, New York State J. Med. **43**:2057-2064 (Nov. 1) 1943; Electrically Induced Convulsions in Treatment of Functional Mental Disease, M. Ann. District of Columbia **10**:163-170 (May) 1941.

3. Ziegler, L., in discussion on Evans, V.: Physical Risks in Convulsive Shock Therapy, Arch. Neurol. & Psychiat. **48**:1017-1020 (Dec.) 1942.

4. Ebaugh, F.; Barnacle, C., and Neubuerger, K.: Fatalities Following Electric Convulsive Therapy, Arch. Neurol. & Psychiat. **49**:107-117 (Jan.) 1943.

5. Cash, P., and Hoekstra, C.: Preliminary Curarization in Electric Convulsive Shock Therapy, Psychiatric Quart. **17**:20-34, 1943.

the trigeminal nerve, there occurred a small softening in which microglia and oligodendroglia cells, in various phases of reaction, were noticeable.

In the basal ganglia, the vascular changes were more pronounced, and blood vessels were undergoing hyaline degeneration. In addition, considerable calcification of blood vessels was noted in the internal capsule and the striatum.

Here and there in the occipital lobe were areas in which metabolic products of disintegration, such as amyloid bodies, were numerous, particularly in the vicinity of the posterior horn of both lateral ventricles.

Of importance in this case was the occasional presence of hematic pigment immediately surrounding the blood vessels. However, fresh hemorrhages, in which red blood cells were still well preserved, were not seen.

About some of the small blood vessels was a slight infiltration, consisting chiefly of lymphocytes.

The problem under discussion in this case concerns the relation of electric shock therapy to the pathologic changes in the central nervous system. The clinical history gave evidence of syphilitic infection, and the neuropathologic changes indicated a form of vascular syphilis, the most probable type of which was the so-called endarteritis of the small blood vessels. Inflammatory changes were few, it is true, but here and there small perivascular infiltrations of lymphocytes were apparent. This manifestation of inflammation, however, was of minor intensity. The meninges disclosed a considerable number of chromatophores, and the blood vessels showed both calcification and hyaline degeneration, all changes in accord with a possible diagnosis of cerebrovascular syphilis.

Only the occasional punctiform hemorrhages could be related to the action of the electric shock. Here, also, the previous involvement of the blood vessels by a pathologic process must be considered, damage which made easier the extravasation of blood. The latter was perhaps related to the first of the two electric shocks, since only blood pigment, and not fresh red blood cells, was to be seen.

With respect to the vascular congestion, asphyxial phenomena preceded death, and the asphyxia was related to congestion of the lungs and may have provoked the vascular distention. The neuropathologic study of this case failed therefore to reveal evidence of any relation between the pathologic changes and electric shock therapy except for the few punctiform hemorrhages, which may have been induced by the convulsive seizure. The entire pathologic picture points to a preexisting pathologic process, presumably of syphilitic origin.

COMMENT

Several investigators have shown, with the aid of laboratory procedures, that electric shock treatment creates a disturbance in cerebral function. Pacella, Barrera and Kalinowsky [6] stated that changes in the electroencephalographic pattern occur in all cases and may persist several months if grand mal convulsions have been produced. Levy, Serota and Grinker [7] claimed that such alterations occur in 50 per cent of treated patients; they agree that the changes may last several months. They stated that changes in intellectual function occur in 45 per cent of cases but declared that mental improvement is not dependent on the presence of such changes, as demonstrated electroencephalographically or by other means.

Alpers and Hughes,[8] in experiments with cats, discovered that hemorrhage, either punctate or of a more extensive character, is the most common lesion and may occur anywhere in the brain. They noted loss of cells and fibers in the region of extravasations. They expressed the opinion that there is no relation between the number of shocks and the severity of changes in the brain. Heilbrunn and Weil [9] made similar observations on rabbits. They noted multiple small hemorrhages throughout the brain, produced by rupture of the vessel walls, combined with edema, injury to ganglion cells and a proliferative glial reaction of the surrounding tissues. They expressed the opinion that the danger of electric shock treatment lies not in generalized destruction of ganglion cells, which they did not see, but in the possibility of multiple hemorrhages, followed by local repair.

Thus far, autopsy reports have seldom been adequate; so one is still groping in the dark. In 1 of the 3 cases for which Ebaugh and his associates tabulated data with autopsy observations, the patient was 75 years old, and there was enough evidence of advanced arteriosclerosis to obscure any pathologic changes that might have been due to the three treatments the patient received. Their own 2 cases had many features in

6. Pacella, B. L.; Barrera, S. F., and Kalinowsky, L.: Variations in Electroencephalogram Associated with Electric Shock Therapy, Arch. Neurol. & Psychiat. **47:** 367-384 (March) 1942.

7. Levy, N. A.; Serota, H. M., and Grinker, R. R.: Disturbances in Brain Function Following Convulsive Shock Therapy, Arch. Neurol. & Psychiat. **47:**1009-1029 (June) 1942.

8. Alpers, B. J., and Hughes, J.: Changes in the Brain After Electrically Induced Convulsions in Cats, Arch. Neurol. & Psychiat. **47:**385-398 (March) 1942.

9. Heilbrunn, G., and Weil, A.: Pathologic Changes in the Central Nervous System in Experimental Electric Shock, Arch. Neurol. & Psychiat. **47:**918-930 (June) 1942.

Electric Shock Treatment.—On Jan. 13, 1943, he received 90 volts for one-tenth second and had a petit mal reaction. He was soon ambulatory and showed no unusual reaction. On January 15 he received 100 volts for one-tenth second and had a typical grand mal convulsion. One hour later he was ambulatory and complained only of nausea and headache. He ate, and later in the morning he returned to his ward, where he was ambulatory. On January 17 he was fed by tube at 10:30 a. m. because he had been eating poorly. He appeared to be comfortable, however, and one hour later was fed by spoon. At noon he took liquid nourishment and engaged one of the nurses in conversation. At this time he had no physical complaints. He was first seen to be in distress at 1 p. m., when he appeared pale and was observed to be turning from his back to his abdomen in a restless manner. He retched and expectorated a little blood-streaked saliva, but did not cough or vomit. He made no complaints and cooperated well. The temperature was 101 F. and the pulse rate 88; respirations occurred at a frequency of 36 a minute and were labored. In a few minutes his eyes took on a glazed appearance, and he stared at the ceiling. At 1:30 p. m. he was moribund, and a few minutes later he died.

Autopsy.—Autopsy was performed by Dr. Reider Trygstad, of the Central Islip State Hospital, two hours after the patient died. The report follows.

General Inspection: The body was that of a Negro aged about 30 or 35. Nutrition was fair and the musculature good. There were no deformities. Rigor mortis had not set in. The conjunctiva was clear, and the pupils were equal and in middilation. There was no edema of the ankles or the face.

Cranial Cavity: The calvarium was of thin, firm bone. The amount of cerebrospinal fluid was decreased. The brain was swollen. The pial vessels were notably injected. The pia mater was thin and transparent. The basal vessels were small and thin walled. Preliminary section showed slitlike ventricles. The brain weighed 1,210 Gm. The pituitary gland and pituitary fossa were normal.

Thorax: The pectoral muscles were an intense red. Both lungs were noticeably expanded and were free of adhesions. When the hand was placed in the thoracic cavity, a frothy, blood-tinged fluid escaped from the mouth. The right lung weighed 1,280 Gm. and the left lung 1,270 Gm. The pleural surfaces were clear. There were no petechiae. Sections of the lungs showed an extensive degree of engorgement of the air sacs, with frothy, slightly blood-tinged fluid. The lungs were otherwise normal. The heart was small and weighed 270 Gm. The epicardial surface of the left ventricle showed a few small petechiae. The valves of the heart, the coronary vessels and the heart muscle appeared normal on section. No clots were present. The aorta and the pulmonary artery were both small in caliber. The circumference of the aortic valve was 8.5 cm. and that of the pulmonary valve 9 cm. The aorta showed no evidence of sclerosis or aortitis, and the larger vessels were normal.

Abdomen: There was no subcutaneous or subperitoneal fat. The serosa of the intestine was moist and glistening. The vessels were slightly injected. The spleen was of average size, and the cut surfaces were of normal appearance. The gastrointestinal tract was normal. The stomach contained about 3 pints (1,500 cc.) of the tube-fed mixture. The mucosa was of normal appearance. The liver was of average size; from cut sections there exuded an increased amount

of blood. The gallbladder contained one stone, which was free. The vessels of the pancreas were slightly injected. The left adrenal gland was of average size and pattern, and the medulla was congested. The right adrenal gland was small, but of normal pattern. The kidneys were of average size; the capsules, especially the capsule of the left kidney, were slightly adherent, and the cortical surfaces were smooth. Cut sections showed normal markings. The urinary bladder contained about 4 ounces (118 cc.) of clear urine. The prostate appeared normal, and the genitalia were hypoplastic.

Summary: The significant changes were edema of the brain, pronounced edema of the lungs and hypoplasia of the circulatory system.

Anatomic Diagnosis.—The probable cause of death was asphyxia, with acute edema of the lungs and brain due to circulatory failure, the result of electric shock therapy.

General Histologic Report.—All of the tissues appeared essentially normal.

Neuropathologic Report.—The brain was studied by Dr. Armando Ferraro, of the New York State Psychiatric Institute and Hospital. His report and discussion follow.

Blocks were taken from various areas of the central nervous system, i. e., the frontal, occipital, parietal and temporal cortex; the basal ganglia; the mesencephalon; the pons; the cerebellum, and the medulla oblongata. The usual neuropathologic technics were used—chiefly the Nissl stain for nerve cells, the Spielmeyer method for myelin sheaths, scarlet red for fatty products of degeneration, the Bielschowsky method for neurofibrils and hematoxylin and eosin for general study.

The impression was that of a pathologic condition of the central nervous system of organic type. The most conspicuous changes seemed to indicate a degenerative process, the result, presumably, of vascular involvement.

The pathologic changes in the vessels were represented by diffuse congestion of varying degrees and, above all, by thickening of the walls of the blood vessels and endarteritis, involving the small blood vessels. Presumably as the result of this pathologic process in the vessels, there was diffuse degeneration of nerve cells in various areas. In these areas, in differing degrees, nerve cells had undergone various types of degeneration—chiefly, however, a process that closely resembled the so-called ischemic change. Occasional nerve cells disclosed chromatolysis and gradual disintegration. This degeneration of nerve cells led to scattered areas with poverty of nerve cells and some disturbance of cytoarchitecture.

As a part of the degenerative process involving the nerve cells were a considerable degree of satellitosis, and, even more important, a conspicuous amount of neuronophagia, in which proliferated glial elements actually invaded cells undergoing degeneration.

Throughout the white matter of the cortex, but varying in intensity, was a definite increase of glial nuclei. The oligodendrocytes seemed to be particularly increased and were accumulated in rows about the blood vessels. Here and there, particularly in the cerebellum and the medulla oblongata, collections of glial nuclei formed the so-called glial nodules. In the medulla oblongata, in the area of the tenth, and particularly the eighth, nerve, there was considerable increase of glial nuclei, and bilaterally, in the area of the descending root of

of some damage suffered by the brain during the shock treatment, but they do not answer satisfactorily the question of the cause of death.

Similarly, in the case presented here the cause of death was obscure. Grossly and microscopically the organs were normal, and the changes in the brain were compatible with longer life. The answer to the riddle may lie in the possibility that in selected cases there occur certain irreversible intracellular changes which no one has yet been able to fathom.

SUMMARY

Of 2 patients whose deaths were associated with electric shock treatment, the first died one week after her fourteenth treatment in a hyperpyretic state associated with status epilepticus. The second patient died two days after his second treatment. Autopsy in the second case disclosed evidence of cerebrovascular syphilis and other changes which were possibly due to the treatment itself. However, the alterations were not sufficient to account for death. A review of some of the pertinent literature indicates that the cause of death after electric shock treatment is still obscure. Selection of patients for treatment should not be indiscriminate, especially in the face of an unpromising prognosis. Electric treatment has attendant serious dangers and should not be given to patients with a history of vascular or cerebral disease.

Central Islip State Hospital.

common, but the significance of the observations suffered in some respects because the patients were 57 years of age. Nerve cell degeneration, of variable degrees, increased gliosis and ischemic changes in scattered cells were noted in both cases. The brain of the patient who had thirteen treatments showed one petechia on gross inspection and an occasional perivascular area of pigment, but no signs of fresh blood, while the brain of the second patient, who received only three treatments, presented none of these changes. The latter, too, showed cellular changes with neuronophagia in the dorsal nucleus of the vagus nerve, together with *Gliarasen*. Both patients, surprisingly, received relatively small doses of electric current.

The pathologic picture in the case reported here, unfortunately, was complicated by the syphilitic process, but it should be kept in mind that there was little inflammatory change. Prior to treatment the Wassermann, mastic and benzoin reactions of the spinal fluid were negative, and the total protein was only 35 mg. per hundred cubic centimeters. The diffuse cellular degeneration, with disturbed cytoarchitecture, the ischemic changes in cells and the increase in glia cells—all of which were noted in the cases reported by Ebaugh and associates—may well have been due to the syphilitic process. Certainly, the perivascular infiltration, the hyaline degeneration of vessels and the amyloid bodies speak for vascular syphilis. Some of these changes may have been due to the intensive treatment with arsenicals in 1939. However, two features of the pathologic process in this brain deserve closer consideration. In the areas of the eighth and tenth nerves "there was considerable increase of glial nuclei, and bilaterally, in the area of the descending root of the trigeminal nerve, there occurred a small softening in which microglia and oligodendroglia cells, in various phases of reaction, were noticeable." Ebaugh and associates reported somewhat similar changes in the medulla of the patient who received three treatments. Consequently, one may surmise that these changes were produced by the electric current, which notably affects the respiratory center, or were already present as a result of the syphilis and were aggravated by the electric treatment. Progressive alterations occurring in the medulla after the second treatment may have resulted in the clinical picture immediately preceding death.

The second feature worthy of close attention is one which Ebaugh and associates noted in 1 of their cases, namely, the presence of perivascular hematic pigment, an indication of the occurrence of punctiform hemorrhages. Hemorrhages of this type were commonly observed in cats and rabbits, but in my second case and in Ebaugh's case fresh hemorrhages were not seen. The presence of perivascular pigment, however, is presumptive evidence of previous hemorrhage, and it may be surmised that the bleeding was the result of the syphilitic process already present in the vessels. Extravasation during a convulsion would conceivably be easier through the wall of a damaged vessel than through the wall of a healthy one. This evidence emphasizes the need of selection for treatment of patients who are free from the taint of vascular, as well as cardiac, involvement. Of course, the patient would not have been treated if the laboratory tests had given positive evidence of syphilis. Perhaps the fact that the Wassermann reaction of the blood was once positive should have been regarded as a contraindication.

No definite conclusion can be drawn with respect to the first case because of the absence of autopsy evidence. However, the acute nature of the patient's death, which followed so closely on her treatment, makes it logical to suspect some connection between the two events. It is possible that in this patient, as in a few of the cats studied by Alpers and Hughes, more extensive hemorrhages occurred in the hypothalamic region, sufficient to cause the hyperpyrexia and status epilepticus. The fact that the patient died one week after her last treatment speaks against this possibility, but the exact time of occurrence of hemorrhage after treatment is not known. Further, it is possible that, among other areas injured, the current produced damage to the cells in the region of the already labile heat-regulating center. These changes could have been associated with punctate hemorrhages and subsequent edema to produce the same result. While it is unwise to speculate too much about this case, I feel that one is only avoiding the issues involved if one disregards this death or attributes it merely to "excitement and exhaustion." Fatalities of this nature warrant continued study.

The fact remains that even after autopsy the cause of death sometimes remains unknown. In the first case reported by Ebaugh and associates death was due to coronary thrombosis, but the cerebral changes, although more extensive than those in their second case, seemed insufficient in themselves to cause death. Of their second case they stated:

. . . . The changes in the brain cannot be considered directly responsible for the death. They are indicative

Neurologic examination revealed signs of meningeal irritation, including positive Brudzinski and Kernig signs. The reflexes were hyperactive in both upper and lower extremities. The Babinski sign was elicited bilaterally. Lumbar puncture revealed grossly bloody fluid. A diagnosis of spontaneous subarachnoid hemorrhage was made. Bleeding continued, and the patient was transferred to another hospital, where he died.

CASE 5.—A white man aged 33, who was known to have been alcoholic for many years, was admitted to the hospital because of characteristic delirium tremens. He had previously sustained an injury to the head of undisclosed severity and had been admitted to another hospital in a state of delirium.

Examination revealed a hematoma of the scalp, unequality of the pupils, which reacted poorly to light, tremor of the upper extremities and a Babinski sign bilaterally. Lumbar puncture showed clear, colorless fluid under normal pressure. However, serologic studies of the blood and spinal fluid gave positive reactions, and the colloidal gold curve was characteristic of dementia paralytica. When the delirium cleared, the patient showed a typical picture of this disease.

It should be noted that 11 patients had an atypical Babinski sign and that of this number 10 had accompanying tremor. This is in contrast to the figures for the other 174 patients in the series, only 73 of whom had tremor.

COMMENT

The mechanism of tremor associated with alcoholism has often been postulated to be cerebellar. In patients in the present series the signs and symptoms pointed to diffuse disorganization of the cortex as playing a part in the production of tremor, possibly through disturbance of the frontopontocerebellar tracts. In some patients the chemical activity of alcohol produced a picture akin to an anxiety state, with fears, apprehensions and coarse generalized tremors. These symptoms, together with the anxiety, disappeared rapidly as the effects of the alcohol diminished. This is in contrast to the picture characteristic of dementia paralytica, Wilson's disease (hepatolenticular degeneration) and other degenerative diseases, in which the tremor is maintained constantly, with only slight moderation by psychogenic factors. We interpreted the Babinski sign as a part of the defense reflex, and eventually as a part of the flexor reflex. Its presence indicates involvement of the corticospinal pathways, on either an anatomic or a functional basis.

The various pathologic syndromes of acute and chronic alcoholism are associated with lesions involving structures from the periphery to the cortex. That persons with considerable evidence of cerebral alteration presented no signs of damage to the pyramidal tract indicates the possibility of selective damage by alcohol to certain parts of the nervous system. Only in patients with evidence of other etiologic factors, such as syphilis of the nervous system, subarachnoid hemorrhage and pellagra, did signs of damage to the pyramidal tract appear. This may be because the main effect of alcohol is on the association tracts, rather than on the great projection fiber system. Mental aberrations, disturbances in speech, tremors and absence of signs of damage to the pyramidal tract may be explained by this hypothesis. A similar picture exists with some of the cortical and mixed degenerative disorders. The fact that patients with the Babinski sign had a higher incidence of tremor suggests more advanced involvement of the central nervous system, with beginning involvement of the projection fiber tracts.

It is noteworthy that in none of the 200 patients studied did the condition resemble the typical Wernicke syndrome, or polioencephalitis hemorrhagica superior (with extraocular palsies, pupillary changes and disturbances in consciousness).

CONCLUSIONS

The extreme rarity of the Babinski sign in patients with uncomplicated alcoholism is evidence that lesions of the corticospinal tract are rarely produced by alcoholism, and its presence should focus the attention of the examiner on factors other than alcoholism.

The absence of signs of involvement of the pyramidal tract in alcoholic patients may indicate selective action of alcohol on the central nervous system. In the cerebrum this action is probably chiefly on the association tracts, rather than the great projection fibers.

Tremor is present in a significant number of alcoholic patients with psychosis but is extremely variable in type and rhythm. Such tremor may be caused by alteration in the frontopontocerebellar mechanism, but sometimes it may be influenced or aggravated by associated anxiety.

Tremor is much more constant in patients who show an atypical Babinski sign than in alcoholic patients in general. This frequency of association might be taken as an indication in such patients of more advanced involvement of the central nervous system, with beginning disturbance in the projection fibers.

None of the 200 patients studied had a condition which answered the description of Wernicke's syndrome, or encephalitis haemorrhagica superior.

Boston Psychopathic Hospital.

TREMOR AND THE BABINSKI SIGN IN ALCOHOLIC PATIENTS

INCIDENCE AND INTERPRETATION

ARNOLD P. FRIEDMAN, M.D., AND JAMES E. ROY, M.D.

BOSTON

Alterations of cerebral function in alcoholic patients are evidenced by confusion, disordered speech and convulsions. In spite of these manifestations of cerebral dysfunction, tremor is not always present, and the Babinski sign is rare. To determine the incidence of tremor and the Babinski sign in alcoholic psychoses, we carefully examined 200 patients, all of whom were addicted to prolonged and excessive use of alcohol in various forms.

MATERIAL AND OBSERVATIONS

The material consisted of 200 adults, ranging in age from 21 to 65, with histories of various degrees of alcoholism, who were admitted to the Boston Psychopathic Hospital between November 1940 and June 1943 for alcoholism. In tests for the Babinski sign, the criteria employed were essentially those laid down by Babinski in *Semaine médicale*. The patient was well relaxed, with the eyes closed, the legs extended and the feet resting on the bed near its outer edge, or with the legs lifted and held by the examiner. In all cases it was ascertained that free movement of the big toe was possible. The stimulation was vigorous and was applied to the outer part of the sole of the foot. A constant extension of the large toe was considered a Babinski sign. Fanning of the toes was not considered an essential part of the Babinski sign in this study.

Of the patients studied, a Babinski sign was elicited in 16, and gross tremor, particularly in the upper extremities, in 87. Of the 16 patients, the Babinski sign was typical and constant in 5 and atypical in 11. An atypical response consisted either in no movement of the great toe or in partial dorsiflexion, occurring unilaterally, while a clearcut normal response was obtained on the other side. Tremor was present in 4 of the patients with a constant Babinski sign and in 10 of the patients with an atypical sign. The 5 patients who exhibited a constant Babinski sign showed additional signs and symptoms, an indication of pronounced abnormalities of the central nervous system. A brief description of the 5 cases follows.

CASE 1.—A white man aged 56 was admitted to the hospital because of visual hallucinations and threatening behavior. He had been drinking heavily since the age of 27 but had stopped three weeks prior to admis-

sion. There was a history of a previous attack of depression. A week prior to admission he became violent, wanted liquor, broke a window, called his sister names and expressed grandiose ideas.

On admission he was restless and overactive, and speech was incoherent and irrelevant. He expressed grandiose delusions, was completely disoriented for time and gave a poor account of his past life. The impression was that of dementia paralytica, but lumbar puncture, including serologic tests, gave negative evidence.

The blood pressure was 200 systolic and 100 diastolic. Neurologic examination revealed atrophy of the left optic nerve, chorioretinitis involving both eyes, absence of the pupillary reflex to light and internal strabismus. There was tremor of both upper extremities. The reflexes were hyperactive in the trunk and the lower extremities, and a Babinski sign was elicited bilaterally.

The patient showed no improvement and was committed to a state hospital at the end of one week.

CASE 2.—A white man aged 50 was admitted to the hospital via the courts because of threats. He had had previous admissions to the hospital for alcoholism and for epilepsy. The epilepsy had been characterized by typical grand mal convulsions occurring at frequent intervals over a period of twenty years. Studies during this time (including lumbar punctures) revealed no cause for the convulsions.

Examination showed tremor of the upper extremities. The reflexes were hyperactive in both the upper and the lower extremities, and a Babinski sign was elicited on the left side. The mental status was not remarkable except for irritability.

CASE 3.—A white man aged 29 was admitted to the hospital because of confusion. He was known to have been alcoholic for several years.

Examination of his mental status on admission showed tremulousness, misunderstanding of commands, disorientation, auditory hallucinations and poor cooperation.

General physical examination revealed a smooth tongue, enlargement of the liver and cutaneous changes consistent with severe avitaminosis. (The changes attributed to avitaminosis disappeared with treatment.) Neurologic examination showed weakness of the extremities, hyperactive reflexes, myoclonic movements of all extremities and a Babinski sign on both sides. Tremors were present in the upper extremities. There were sweating, coldness and cyanosis of the hands and feet. A few days after admission he had epileptiform seizures of tonic type ("cerebellar fits").

CASE 4.—A white man aged 56 was admitted to the hospital because of confusion and increased activity. Three days prior to admission he fell unconscious. He was removed to another hospital, where he was confused, complained of headache and, after medication, attempted to sever his penis. He was known to have been alcoholic for several years.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Anatomy and Embryology

AN EXPERIMENTAL STUDY ON THE ORIGIN OF THE SENSORY NEURONES AND SHEATH CELLS OF THE IXTH AND XTH CRANIAL NERVES IN AMBLYSTOMA PUNCTATUM. C. L. YNTEMA, J. Exper. Zool. **92**:93 (Feb.) 1943.

Previously described experimental methods were used in the investigation of the origin of the glossopharyngeal and the vagus nerve The ninth and tenth lateral line ganglia arise from dorsolateral placodes, while the visceral ganglion of the ninth nerve comes from the second epibranchial placode. The anterior visceral ganglion of the tenth nerve arises from the third and fourth epibranchial placodes, and the posterior visceral ganglion of the tenth nerve, from the fifth epibranchial placode.

The postbranchial neural crest, which is medial to the fourth and fifth somites, gives rise to the root ganglion of the tenth nerve, while from the neural crest which lies medial to the anterior part of the sixth somite arises the ganglion of the third spinal nerve.

Sheath cells on the roots of the ninth and tenth nerves arise from the neural crest at the levels of the origins of the various roots. Sheath cells on these nerves and their branches are derived from both neural crest and placodal ectoderm. REID, Boston.

Physiology and Biochemistry

CHOLINESTERASE AND THE BEHAVIOR PROBLEM IN AMBLYSTOMA. CHARLES H. SAWYER, J. Exper. Zool. **92**:1 (Feb.) 1943.

A close correlation between the cholinesterase content and functional ability as expressed by behavior was revealed by a quantitative study of the development of the enzyme content throughout the larval life of Amblystoma punctatum. A method of alkalimetric microtitration of the acetic acid liberated on the hydrolysis of acetylcholine was used. This method was sensitive to 5×10^{-9} mols of ester (0.9 micrograms of acetyl choline chloride).

The small amount of the esterase found in the premotile embryo did not increase during the early flexure and coil stages but rose sharply at the beginning of the nontetanic S flexure stage. The enzyme continued to increase during the period of the more rapid movements of the swimming stages.

Larvae reared in solutions of cholinesterase inhibitors showed profound changes in physiologic activity, which were found to depend on the degree of inhibition of the enzyme. On removal of the animal from the inhibitor solution the recovery of physiologic capacity and that of enzymic activity paralleled each other.

The author concludes that cholinesterase content is a biochemical criterion of functional capacity in the neuromuscular apparatus and that the physiologic development of this system can be quantitatively assayed in terms of its esterase activity. REID, Boston.

EFFECT OF 180 DEGREE ROTATION OF THE RETINAL FIELD ON VISUOMOTOR COORDINATION. R. W. SPERRY, J. Exper. Zool. **92**:263 (April) 1943.

In 15 newts both eyeballs were rotated 180 degrees on the optic axis, the optic nerves being left intact. In 14 newts only one eyeball was rotated, while the other eye was either excised or left in the normal position. This rotation resulted in complete inversion and reversal of visual perception, which was manifest in deliberate erroneous reactions and various abnormal performances directly related to retinal rotation. There was also a dorsoventral reversal in chromatophoric adaptation.

The animals with reversed vision were at a greater disadvantage than the totally blind control newts. The maladaptive visuomotor coordinations persisted in all cases during the four and a half months of the test period, without any sign of inhibition or correction by reintegration of the central nervous system.

The results demonstrate a rigidity of mechanisms for central coordination in the visuomotor system of urodeles comparable to the implasticity of spinal organization present in amphibians and rats. REID, Boston.

THE EFFECT OF PROSTIGMINE AND ACETYLCHOLINE ON DENERVATED MUSCLE. RUDOLF ALTSCHUL, J. Nerv. & Ment. Dis. **97**:549 (May) 1943.

Although there are theoretic reasons for the employment of prostigmine with other diseases of the central and peripheral nervous systems, its use has been accepted only in treatment of myasthenia gravis and postoperative paresis of the bowel and bladder. With the idea of testing the value of the drug in treatment of injuries of the motor nerves, the author attempted to determine the effect of injections of prostigmine and acetylcholine in hastening recovery from lesions of the lower motor neuron. In 18 animals (8 cats and 10 rabbits) the lateral popliteal nerve, and in some animals the sciatic nerve also, was avulsed and treatment started immediately with intramuscular injections of prostigmine methylsulfate (in a dose of from 0.2 to 0.6 cc. of a 0.5 per cent solution) and subcutaneous injections of acetylcholine (from 0.00025 to 0.0065 Gm.). The effect of treatment was judged clinically by observation of the spreading reflex of the toes and anatomically by loss of weight of the innervated muscle and by histologic examination of the severed nerve trunk and atrophic muscle.

There was no clear difference in loss of weight between muscles of treated and those of untreated animals. Histologic changes in the denervated muscles were greater in the controls than in the treated animals and greater in the rabbits than in the cats. The proliferation of connective tissue which would be expected in atrophic muscle was slight or absent in treated cats. Thus, histologic comparison of the denervated muscles in cats showed greater changes in the untreated than in the treated animals, but as measured by loss of weight the difference was not apparent. No such results were obtained in the rabbits. In addition, there were notable differences in the reactions to the drugs of different animals of the same species, while various muscle groups also reacted differently. The author believes that experiments of this type should be repeated, if possible with larger doses of acetylcholine. CHODOFF.

406

Clinical Notes

A SIMPLE AUTOMATIC PNEUMOENCEPHALOGRAPH

CAPTAIN RAYMOND L. OSBORNE, MEDICAL CORPS, ARMY OF THE UNITED STATES

That air appears as a contrasting medium in the ventricles of the brain in roentgenograms of the skull was accidentally discovered by Luckett,[1] in 1913. Dandy,[2] in 1918, was the first to use air intentionally, when he introduced the gas directly into the ventricles. In 1919 he[3] injected air into the lumbar subarachnoid space to outline cerebral structures on the roentgenogram. This procedure he called encephalography. To avoid confusion with electroencephalography, it may better be designated as pneumoencephalography. If no block exists, the pneumoencephalographic method provides for admission of air into any intracranial space occupied by cerebrospinal fluid.

TECHNIC

In this paper there is described a simple automatic pneumoencephalograph which can be improvised from materials usually at hand in any hospital. Any two receptacles, a length of rubber tubing and one of glass, two lumbar puncture needles and two needle adapters comprise all that is necessary. Two empty Baxter Vacoliter infusion flasks are ideal, but fruit jars with suitable rubber stoppers will do, provided they are made air tight. The material is arranged into the system illustrated in the accompanying figure.

The patient is placed in a sitting position, leaning forward against the back of an inverted chair, which is cushioned with pillows. A double rachiocentesis with two needles is performed at the fifth and the fourth or third lumbar interspace in the usual way. The pneumoencephalographic system is filled with oxygen[4] by passing the gas through from 1 to 7, and then the rubber tubing is closed off by pinching or with hemostats placed at 1 and 7. Now tube 1 is attached by its glass adapter, a, to needle A, and a little cerebrospinal fluid is allowed to run into the bottle C. If it is desired

1. Luckett, W. H.: Air in the Ventricles of the Brain Following a Fracture of the Skull, J. Nerv. & Ment. Dis. 11:326, 1913.

2. Dandy, W. E.: Ventriculography Following the Injection of Air into the Cerebral Ventricles, Ann. Surg. 68:5, 1918.

3. Dandy, W. E.: Roentgenography of the Brain After the Injection of Air into the Spinal Canal, Ann. Surg. 70:397, 1919.

4. Atmospheric air or various gases may be used. Oxygen is preferable because it is absorbed rapidly and is less irritating.

to draw off more fluid than air,[5] the desired quantity may be drained off from the open needle before the system is connected. Then tube 7 is similarly attached to needle B by its adapter, b. The operation is then completed.

Now each drop of fluid displaces gas from bottle C, passes it through glass tube 3, rubber connection 4 and glass tube 5 and washes it free of dust and contaminant in the water trap. The gas then bubbles out tube 6 and rubber connection 7 and into the intrathecal space through needle B. Since fluid is heavier than gas, gravity draws the cerebrospinal fluid down and allows the gas to rise; thus fluid continues to drain out of needle A and the gas to pass in through needle B. The gas accumulates in the subarachnoid system of the skull
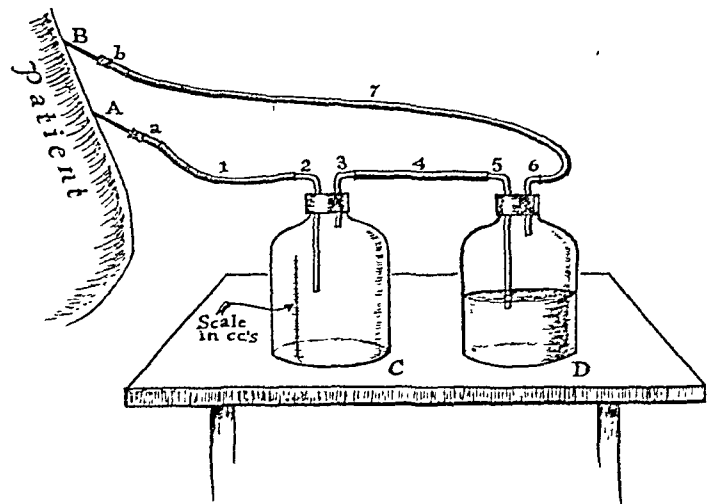
Drawing of the pneumoencephalographic apparatus.

and displaces more fluid down and out. The procedure is completed when the automatic system stops operating, for the subarachnoid space is then drained. The roentgenogram is then taken immediately.

ADVANTAGES

In the closed method there is less mechanical change in the subarachnoid space; fluid is displaced drop by drop, not ounce by ounce, and intrathecal pressure fluctuates little. The headache following the procedure is less severe and the postoperative course shorter. After the machine is connected and running, the operator may observe his patient, for his hands are free. The machine will automatically complete the procedure and stop itself. The apparatus costs nothing, for it is made of scrap materials found in any hospital.

5. Gas expands in volume with increase in temperature, in accordance with the Gay-Lussac law; therefore many operators draw off more cerebrospinal fluid than the volume of the gas they admit to the subarachnoid space.

405

When viewed from this approach, certain schizophrenic symptoms become understandable. Thus, some of the strange words used by the schizophrenic patient are comprehensible when they are considered in relation to the concrete situation which the patient experiences at the moment. There is an absence of generic or categorical words. Goldstein believes that peculiarities of language associated with schizophrenia have been erroneously considered as expressions of symbolic or metaphorical thinking. To understand the language of schizophrenic persons, the observer must discover and understand the special concrete situations in which the patient is living.

Another difficulty in the thinking of schizophrenic patients, as in that of patients with organic lesions of the brain, is loss of constancy and definiteness in the conception of the structure of objects. This is ascribed to impairment of the "normal" figure-ground formation, to the patient's inability to place the proper significance in the figure part of experience and abstract it from the ground. Many illusions and delusions of schizophrenic persons originate in this way, since, owing to deficient figure-ground formation, objects or situations which can be grasped as concrete come abnormally into the foreground and the patient gives an answer which appears to the normal person as a defect in recognition. An outstanding symptom is the disappearance of the normal boundaries between the ego and the outer world.

Although Goldstein believes that equivalent functional changes can be produced by organic and by psychologic derangement, he does not draw conclusions as to the identity of the underlying processes in organic disease and in schizophrenia. While both conditions show impairment in the attitude toward the abstract, the trend toward the concrete in patients with somatic disturbance is of a more simplified and inane form than that of the schizophrenic patient, which has a richer and more individual flavor.

Whether the impairment toward the abstract associated with schizophrenia is a primary or a secondary phenomenon cannot be definitely stated. The similarity in the changes in patients with organic disease and those in schizophrenic patients points to the probability that a *somatic factor is involved in schizophrenia.*

As long as the impairment persists in the attitude toward the abstract, the usual psychotherapeutic procedure is doomed to failure. Thus a more direct, concrete communication with the patient, based on empathy and cooperation with him, is necessary. Shock therapy may be able temporarily to lift the impairment and permit psychotherapy to be effective. It is at this time that the battery of tests employed by the author may be useful in indicating the accessibility of the patient and the type of psychotherapy to be employed.

CHODOFF.

NOTES ON THE PERSONALITY OF PATIENTS WITH MIGRAINE. LOWELL S. TROWBRIDGE, DOROTHY CUSHMAN, M. GENEVA GRAY and MERRILL MOORE, J. Nerv. & Ment. Dis. 97:509 (May) 1943.

Migraine is a symptom complex rather than a disease, occurring frequently in otherwise healthy persons, often of high intelligence, and showing a strong familial tendency. In addition, there is the suggestion of an arrest in psychosexual development in many subjects with the disturbance. Of 37 women with the disorder who were studied by the authors, not one had made a successful heterosexual adjustment, and in all the libido appeared to be weak or poorly organized. The 13 men who were included in the series were reticent in discussing sexual adaptation and seemed to be lacking in

sexual curiosity. Headaches first appeared at that moment in life when the victim was faced with an initial adult responsibility. The migrainous patient is deliberate in judgment, often indecisive, insecure, perfectionistic and compulsive, sensitive, anxious and quickly discouraged. Fromm-Reichmann expressed the belief that persons with migraine suffer from unresolved ambivalence and that in their effort to repress their hostility toward loved persons they convert it into the characteristic symptoms. The authors feel that the histories of their patients are similar to those of patients with frank psychoneuroses and of persons who are extremely maladjusted, and they suggest that the individual patient displayed his particular symptoms either because of his migrainous constitution or because his predisposition to migraine was activated by his special problems. Despite some belief to the contrary, there is no evidence that migraine affects brain workers more than laborers.

The Bell adjustment inventory, given to 4 male and 12 female patients suffering from migraine, revealed that they were normally adjusted to their homes, unsatisfactorily adjusted with regard to health, timid and retiring, poorly adjusted emotionally and well adjusted in their occupational environment. From these results it is seen that the migrainous patient tends to be similar to the psychoneurotic patient and that psychotic trends are absent.

CHODOFF.

PEYOTE INTOXICATION. WALTER BROMBERG and CHARLES L. TRANTER, J. Nerv. & Ment. Dis. 97: 518 (May) 1943.

Peyote (Lophophora Williamsii and Anhalonium Lewinii) is a small, greenish cactus containing at least nine alkaloids. Its use produces characteristic physical, mental and visual phenomena of a universal type. With peyote intoxication there occurs an incessant flow of visions of infinite beauty, of both color and form, followed by horrible and grotesque appearances. The sense of time is lost, and after a time feelings of religious exaltation may appear. Two distinct types of reactions occur in the same person. In one, there are nausea, anxiety, feelings of bodily change, with fear of dissolution, and frightful visions; in the other, a feeling of religious peace and contentment and euphoria. The sensations experienced resemble those derived from the smoking of marihuana. The anxiety felt as an initial effect with both drugs can be ascribed to changes in proprioceptive perceptions, with consequent damage to the "body image." The addition of visual hallucinations causes an increase in the fright reaction, approximating panic. These hallucinations are zooscopic and reminiscent of delirium tremens. At times the peyote-induced anxiety reactions merge into a psychotic picture.

The cult, or religion, of peyote among the Indians of the Southwest (Piutes, Utes and Navajos) has as its essence the conferring of power by Father Peyote on all its adherents—power to cure illness, bad habits and idleness. In their combat with deep, unconscious anxieties, the Indians, constantly battling a stern and harsh nature, found peyote an instrument for making life tolerable through its conferring on a man power which he would not otherwise possess. The religion also serves the secondary purpose of hiding from public view a sense of inferiority engendered by a clash of cultures. It is through these psychologic mechanisms, as well as by a direct effect on the cerebrum and the thalamus, that the secondary stage of euphoria and contentment is produced in the Indian user of the drug.

CHODOFF.

Neuropathology

OLIGODENDROGLIOMATOSIS OF THE CEREBROSPINAL PATH-
WAY. DIANA J. K. BECK and DOROTHY S. RUSSELL,
Brain **65**:352, 1942.

In recent years oligodendrogliomas, which in the
past were regarded as benign, have been observed by
several investigators to take on malignant features.
Beck and Russell report 4 instances of metastatic spread
of an oligodendroglioma along the cerebrospinal path-
way. In these 4 cases the tumor spread diffusely
throughout the subarachnoid spaces, including those of
the spinal cord in the 3 instances in which the cord was
examined. The primary tumor abutted on the ven-
tricular system in all but 1 case. Dissemination of the
tumor cells was spontaneous, though it was probably
accelerated by operative intervention in 1 case. In the
latter case ventriculographic examination revealed dila-
tation of the lateral and third ventricles before opera-
tion, and it may therefore be inferred that meningeal
deposits were already present at this time. Two of the
4 cases reported were those of children, the shortness
of the clinical history and the macroscopic appearance
of the meninges being reminiscent of medulloblastoma.
The adults had a longer history and the macroscopic
change in the meninges strongly resembled chronic
arachnoiditis. In all 4 cases the length of the clinical
history was, in fact, directly proportional to the degree
of meningeal fibrosis. Oligodendrogliomas, therefore, may
vary widely in their behavior. They may proliferate as
actively as any of the more malignant gliomas; on the
other hand, the metastases may undergo little active
proliferation, but promote, rather, meningeal fibrosis.

Diffuse mucinous change in the stroma in oligoden-
drogliomas is pointed out as of diagnostic importance,
a special search in other types of metastasizing gliomas
failing to reveal evidence of mucin.

Clinically, a variable degree of hydrocephalus
occurred in all cases in which the cerebrospinal fluid
pressure was persistently high. The protein content of
the fluid was high, but few cells were noted. There
was remarkably little involvement of cranial nerves,
considering the extensive infiltration at the base of the
brain. However, the first and second cranial nerves
were affected in 3 cases.

High voltage roentgen therapy failed to confer any
benefit in 3 cases. This accords with the increasingly
prevalent opinion that the oligodendrogliomas, as a
class, are not susceptible to irradiation.

SHENKIN, Philadelphia.

Psychiatry and Psychopathology

CLINICAL STUDIES IN SCHIZOPHRENIA. C. MACFIE
CAMPBELL, Am. J. Psychiat. **99**:475 (Jan.) 1943.

Campbell studied 9 patients who manifested schizo-
phrenic surrender. The outstanding factors in this
group were the constitutional inadequacy and the un-
favorable external factors. No physical factors could
be elicited which satisfactorily explained the deteriora-
tion. Campbell noted that in the course of deterioration,
when superior functions fell into abeyance, reactions of
a lower neurologic order appeared. No special mani-
festation of basic urges was evident, and the condition
was one of defect rather than of conflict. The patients
surrender and accept life at a lower, automatic level.
This surrender is the response of underprivileged,
frustrated persons to the challenge of life.

FORSTER, Philadelphia.

STUDIES ON THE PROGNOSIS IN SCHIZOPHRENIC-LIKE
PSYCHOSES IN CHILDREN. R. S. LOURIE, B. L.
PACELLA and Z. A. PIOTROWSKI, Am. J. Psychiat.
99:542 (Jan.) 1943.

Lourie, Pacella and Piotrowski studied 20 children
who at some time before the age of 12 years experienced
psychotic episodes classifiable as schizophrenia of child-
hood. The group comprised 15 boys and 5 girls who
presented a psychotic picture characterized by deteriora-
tion from a previous level. The average period of hos-
pitalization was ten months. The average follow-up
period was eight years. At the end of the periods of
observation the following levels of adjustment were
observed: An apparently normal adjustment had been
made by 4 patients; fair to borderline adjustments, by
5 patients, and low grade adjustments, by the remaining
11 patients. Of the last group, 3 manifested reactions
of adult schizophrenia, 5 maintained their level at the
time of hospitalization or deteriorated further and in 3
an organic basis was established. In the vegetative
sphere, it was striking that all patients who failed to
improve remained physically infantile. Anxiety, when
associated with resignation, was of poor prognostic sig-
nificance. Psychometric data with regard to intellectual
and perceptual assets offered prognostic aid. The pa-
tients capable of cooperation in the Rohrschach tests
showed improvement. Electroencephalographic studies
showed no definite correlation with the psychotic picture.

FORSTER, Philadelphia.

THE SIGNIFICANCE OF PSYCHOLOGICAL RESEARCH IN
SCHIZOPHRENIA. KURT GOLDSTEIN, J. Nerv. &
Ment. Dis. **97**:261 (March) 1943.

Goldstein points out that a mental change is charac-
teristic of schizophrenic patients but that not all patients
with a condition clinically diagnosed as schizophrenia
show it. Psychologic investigation may be able to
differentiate patients exhibiting this change and thus
indirectly aid in prognosis. Psychologic studies, more-
over, may be of aid in evaluation of the quality of
recovery after treatment and may serve to indicate the
need of further psychotherapy.

Earlier work of this nature emphasized minute anal-
ysis of single psychologic capacities rather than the
experimental study of changes in the total personality,
which is the modern trend. From studies of the latter
type on persons with lesions of the brain, Goldstein
distinguishes between two kinds of human behavior, the
abstract and the concrete. These are considered as
capacity levels of the total personality, concrete behavior
being realistic, stimulus bound and immediate, while
abstract behavior is detached, categorical and concep-
tual. There are various degrees of each kind. The
healthy person combines the two types of behavior and
can shift voluntarily from one to the other. In certain
diseases of the brain the capacity for abstract behavior
is impaired, and the patient's behavior becomes reduced
to a concrete level. This is considered as the character-
istic change in patients with injury to the brain.

Employing the same general concept, Vigotsky de-
vised a sorting test through the use of which he ob-
served a similar impairment of the attitude toward the
abstract in schizophrenic patients. In his work with
such subjects, Goldstein prefers to use a battery of
tests, including a modification of the Kohs block de-
signs. His results are in agreement, in principle, with
those of Kasanin and Hanfmann, and of Cameron,
namely, that some schizophrenic patients present a
characteristic impairment of the attitude toward the
abstract.

Diseases of the Brain

OPTOCHIASMIC ARACHNOIDITIS. EDWARD R. RYAN, Arch. Ophth. **29**:818 (May) 1943.

Ryan reports 3 cases of chiasmic arachnoiditis, confirmed at operation, in which the symptoms were different.

Of the 3 cases, the first offered a difficult problem in diagnosis. The case was that of 7 year old boy with but one complaint—progressive impairment of vision for two years. The bilateral central scotomas and the atrophy of the optic nerves were accompanied by roentgenographic evidence of destruction of bone in the posterior wall of the right orbital canal, with a normal sella turcica. Operation did not improve the patient's visual acuity.

The second case was that of a 9 year old boy whose only complaint was poor vision in the right eye for three months, with rapid progression of the process during the month before examination. The only signs were papilledema in the right eye, with extensive depression of the visual field in that eye, more advanced in the temporal half, and pronounced depression of the field in the left eye. The diagnosis was confirmed surgically. After operation the fields of vision widened to a notable degree, and vision in the right eye improved from 0.1, prior to operation, to 0.4, after operation; in the left eye vision after operation was slightly less than that present before surgical intervention. Secondary optic nerve atrophy became established after the operation.

In the third case, that of a man aged 34, examination showed normal fundi with bitemporal field defects, more pronounced on the right side. The sella was normal, but the optic foramens were pathologic. The right optic foramen measured 5 by 6 mm., and its margins were decalcified; the left optic foramen measured 4.5 by 4.5 mm., and the margins were clear. After operation and confirmation of the diagnosis, the fields showed an enormous expansion on both sides.

SPAETH, Philadelphia.

MICROPSIA AND TELEOPSIA LIMITED TO THE TEMPORAL FIELDS OF VISION. MORRIS B. BENDER and NATHAN SAVITSKY, Arch. Ophth. **29**:904 (June) 1943.

Bender and Savitsky report a verified case of epidermoid in the chiasmal region, in which the temporal fields of vision presented island-like areas of micropsia and teleopsia and, in addition, a tendency to rotate the plane of the image though the last-mentioned phenomenon was not as sharply limited to the temporal field as were the first two. As a matter of fact, the metamorphopsia was best seen in the apparently normal nasal field.

The case is interesting in that it illustrates specific visual defects in the fields of vision which indicates that the origin of the optic disturbance was peripheral rather than in the occipital cortex.

SPAETH, Philadelphia.

CEREBRAL AIR EMBOLISM. LEO RANGELL, J. Nerv. & Ment. Dis. **96**:542 (Nov.) 1942.

Rangell reviews the literature on the postpartum occurrence of air embolism, especially after the assumption of the knee-chest position during the puerperium. He reports what he believes to be the first case of nonfatal cerebral air embolism following assumption of the knee-chest position. The embolism occurred during the seventh postpartum day in a woman aged 24 and was marked by sudden loss of consciousness, followed by jacksonian convulsions and later by a psychotic state.

The patient was hallucinated, felt herself floating and described everything as rotated at exactly 90 degrees. Abnormal neurologic signs were few. The patient made a complete recovery. The symptoms were thought to be the result of cerebral air embolism following the introduction of air into the circulation through the dilated and patent uterine veins.

The author discusses the arterialization of intravenous air and cites several cases from the literature in which, post mortem, air was observed in the left side of the heart and in the cerebral circulation. He concludes that the air in these cases and in his own case must have passed from the venous to the arterial circulation across the barrier of the pulmonary capillaries.

The symptoms of cerebral air embolism vary widely in individual cases and depend on such factors as the location, number and size of the vessels involved, the extent of the collateral circulation and the importance of the centers supplied by these vessels. Symptoms which have been reported include hemiplegia, monoplegia, convulsions, syncope, vertigo, amaurosis, aphasia, alexia and psychosis. The production of symptoms is due primarily to acute cerebral ischemia, sometimes complicated by perivascular hemorrhages. Therapeutic measures, to be successful, must be instituted almost immediately. They should include efforts toward prevention of further ingress of air, administration of cardiac stimulants and direct removal of air from the right side of the heart. Venesection may be useful. The introduction directly into the right side of the heart of 2 cc. of a solution of epinephrine hypochloride (1 : 10,000 to 1 : 1,000) has been suggested. As prophylaxis, the knee-chest exercises used during the postpartum period are contraindicated. CHODOFF.

ACUTE CRANIOCEREBRAL TRAUMA. F. S. GURDJIAN, J. E. WEBSTER and H. ARNKOFF, Surgery **13**:333, 1943.

The authors report the results of observations at autopsy in 151 cases of death following cranial trauma. The series represents a consecutive, unselected series from the Wayne County morgue, Detroit. Gross evidence of cerebral damage was present in every case, though it was minimal in several instances. In 61 of 133 cases the patient was dead on admission to the hospital, and in 36 instances death occurred within twenty-four hours. The authors confirm the observation that mortality from head injury rises as age increases.

Contusion of the brain was more frequent on the orbital surface of the frontal lobe and over the frontal and temporal poles. There were 191 areas of contusion in 72 of the cases reported. Petechial hemorrhages were noted on gross examination in 54 cases. There were 22 instances of acute subdural hematoma, 11 cases of epidural hemorrhage and 1 case of chronic subdural hematoma, representing a total of 21.5 per cent of the entire group of 151 cases studied. These 34 lesions were of sufficient size to be regarded as operable. The authors conclude that hemorrhage producing a cerebral mass lesion is frequent after trauma. Hemorrhages of nonsurgical magnitude (under 30 Gm.) were observed in the subdural space in 12 additional cases and in the epidural space in 4 more cases. They were observed in the frontoparietotemporal region in 30 of 34 cases of subdural hemorrhage and in 8 of 11 cases of epidural bleeding. In all the cases of surgical subdural hematoma the lesion was unilateral. Fracture of the skull was present and on the same side as the lesion in all cases of epidural hemorrhage; it was commonly absent with subdural hematoma. In 8 cases it was found that the subdural hematoma was on the

EVALUATION OF COMPLAINTS AFTER HEAD INJURY. OTTO KANT, J. Nerv. & Ment. Dis. **97**:542 (May) 1943.

Kant points out the difficulty of determining whether post-traumatic complaints are the direct effect of concussion or are due to a superimposed traumatic neurosis. Encephalographic and electroencephalographic studies are of limited help. Although the main complaints, headache, dizziness, irritability and inability to concentrate, are the same whether they are of somatogenic or of psychogenic origin, it is of great importance to differentiate between the two categories, since the former requires indulgence and curtailment of activities, while persons with psychogenic disturbances should be encouraged to discard their complaints and increase their activities.

In the absence of objective signs of damage to the brain, the examining physician must depend on the patient's subjective account of his complaints and their causal relation to the injury. To evaluate the symptoms properly it is important to determine their place in the setting of a given personality. Just how the symptoms express themselves is as important as their nature.

With somatogenic symptoms the personality as a psychologic phenomenon is not involved at all. Such symptoms lack all expressive quality, are little influenced by interference in the psychologic sphere and give the impression that the personality itself is not involved. They appear "foreign" to the personality and give an impression of genuineness, as opposed to psychogenic symptoms, which have expressive value, appear somewhat nongenuine and are characterized by changeability and suggestibility toward psychologic interference.

The patient with a somatogenic disorder tends to belittle his complaints, while the patient with a psychogenic condition exaggerates his suffering. The former is irritable in outbursts, without apparent reference to his emotional situation, while the latter appears gradually to work himself up into a temper tantrum.

Patellar and ankle clonuses may appear with both types—with the organic form clonus is of constant rhythm and amplitude, while with the functional type it is characterized by crescendo and decrescendo and by sudden interruptions. The influence of distraction is of value in differentiation of a Romberg sign of psychogenic and one of somatogenic origin. The former can often be made to disappear by a sudden, harsh command or by having the patient exercise with his arms.

Actual scores in intelligence tests are of no value in the differential problem, but the method by which the patient achieves his score is of importance. Exaggeration and dramatization of a defect are characteristic of the psychogenic type, as is the contrast between the patient's inability to carry out simple intelligence tasks and his excellent orientation and practical judgment in the ward. Genuine fatigability of somatogenic type shows a steady curve of decline of importance, while that of the psychogenic type is sporadic. CHODOFF.

A STUDY OF THE PERSONALITIES OF TWO HUNDRED AND EIGHTY-NINE ABNORMAL DRINKERS. WILLIAM FLEESON and EDWIN F. GILDEA, Quart. J. Stud. on Alcohol **3**:409 (Dec.) 1942.

Fleeson and Gildea point out that there are three groups of abnormal drinkers, with certain differences existing among them. These groups are designated as follows: 1. Primary addicts. These are abnormal drinkers who use alcohol as an aid in adjustment to their environment and are unable to give up its use in spite of insight. It was found that the average age of such drinkers at the time of admission to the hospital

was lower than that of the other two groups. The incidence of addicts who were without psychoses on admission was higher than that of the other drinkers. A great predominance of psychopathic personalities was noted among this group. Polyneuropathy was found to be twice as frequent among addicts as among symptomatic drinkers. 2. Symptomatic drinkers. Drinking in this group is evidence of a deep-seated maladjustment, which may break through at any time in the form of a clearly defined clinical entity, such as schizophrenia, epilepsy or manic-depressive psychosis. 3. Exogenous drinkers. The drinking of this group is primarily determined by exogenous factors, such patients presenting recognizable signs of chronic overindulgence in alcoholic beverages. Signs of prolonged drinking are deterioration of personality, delirium tremens and the Korsakoff syndrome. Persons with chronic alcoholism drink for various reasons, but by and large because their associates do and they are able to make personality adjustments to their drinking habits even though they show physical signs of overindulgence. They break down with psychoses or near psychoses, lose control of themselves and are sent to the hospital.

LESKO, Bridgeport, Conn.

NEUROPSYCHIATRIC PROGRAM FOR A REPLACEMENT TRAINING CENTER. LELAND E. STILLWELL and JULIUS SCHREIBER, War Med. **3**:20 (Jan.) 1943.

Stillwell and Schreiber present a clearcut and effectively used neuropsychiatric program in a replacement training center. The setup is as follows: 1. A ward is maintained in the station hospital where patients requiring hospitalization for neurologic or psychiatric disorders are studied and cared for until proper disposition is made. 2. A neuropsychiatrist is available for consultation with the other physicians at the hospital. 3. A special training unit is maintained, to which are sent the following types of men: (*a*) mentally normal soldiers who are naturally slow in learning or who manifest poor coordination, (*b*) illiterate soldiers, (*c*) soldiers with language problems, (*d*) soldiers with oligophrenia, (*e*) soldiers with psychoses, (*f*) soldiers with psychopathic personalities, (*g*) neurotic soldiers and (*h*) soldiers with physical disorders.

Any soldier proposed for the special training unit is seen by the psychiatrist together with representatives of the special training unit and of the personnel section in order that his suitability for special training may be determined.

4. A neuropsychiatrist maintains a clinic to which any unit commander may send any of his soldiers whom he considers to be suffering from a personality disorder. From time to time unit commanders are given talks to instruct them in the manifestations of neuropsychiatric disorders.

5. Close cooperation exists between the military police and the neuropsychiatrist in order that chronic guardhouse residents may be studied. Red Cross workers are of valuable assistance in obtaining social data and other pertinent material.

6. The neuropsychiatrist helps to see that morale is maintained. The best means is the provision of a systematic program of education as to the fundamental issues of the war and the arousal in the soldier of a social consciousness, such as he had never known before. Men who are imbued with a zeal which springs from a full knowledge of what they are fighting for are less apt to experience emotional disturbances or other personality disorders as a result of actual warfare.

PEARSON, Philadelphia.

News and Comment

APPOINTMENT OF DR. S. EUGENE BARRERA

The Albany Medical College and the Albany Hospital announce the appointment as of Jan. 1,. 1944 of Dr. S. Eugene Barrera as professor of neurology and psychiatry and neurologist and psychiatrist-in-chief. The professorship of neurology and psychiatry carries with it the directorship of the department of neurology and psychiatry and of Mosher Memorial, which is the psychiatric unit within the department. Dr. Barrera was formerly principal research psychiatrist of the New York State Psychiatric Institute and Hospital, and also assistant professor of psychiatry of Columbia University College of Physicians and Surgeons. In the new appointment, he succeeds Dr. D. Ewen Cameron, who becomes professor of psychiatry at McGill University, Montreal, Canada. Dr. Barrera has been the author and co-author of numerous papers on neurologic and psychiatric subjects.

NATIONAL COMMITTEE FOR MENTAL HYGIENE

The National Committee for Mental Hygiene announces the establishment of a fund for research in psychosomatic medicine. The purpose will be to stimulate and subsidize research in the psychosomatic aspects of the diseases chiefly responsible for disability and death. The fund will be .directed by Dr. Edward Weiss. Projects will be considered by the following committee: Dr. Charles M. Aldrich, Dr. Franz Alexander, Dr. Stanley Cobb, Lieutenant Colonel William C. Menninger and Dr. John Romano. The fund will be administered under the direction of Dr. George S. Stevenson, National Committee for Mental Hygiene.

Communications should be addressed to Dr. Edward Weiss, 269 South Nineteenth Street, Philadelphia 3.

THE AMERICAN BOARD OF NEUROLOGICAL SURGERY

The following candidates, who previously passed the examination for membership in the American Board of Neurological Surgery, have now met the Board's requirement of two years' practice in neurologic surgery and have received their certificates, as of March 26, 1944:

Dr. James G. Arnold Jr., Baltimore; Dr. Samuel Lowis, Boston; Lieut. William Nosik (MC) U.S.N.R.; Lieut. Axel Olson (MC) U.S.N.R.; Capt. James L. Thomson, Medical Corps, Army of the United States, and Dr. C. Robert Watson, Brooklyn.

THE AMERICAN BOARD OF NEUROLOGICAL SURGERY

The American Board of Neurological Surgery will hold an examination on June 5, 1944 at the Illinois Neuropsychiatric Institute, 912 South Wood Street, Chicago.

CORRECTION

In the article by Dr. Robert Wartenberg entitled "Studies in Reflexes: History, Physiology, Synthesis and Nomenclature: Study I," in the February issue (ARCH. NEUROL. & PSYCHIAT. 51:113, 1944), the following corrections should be made:

On page 115, second column, in the seventh line from the top, the word "reflex" should be "reflexive."

On page 132, first column, in the third line in the first paragraph under the center head "Finger-Thumb Reflex (Mayer)," "metacarpophalangeal reflex" should be changed to "basal joint reflex."

On page 133, fifth line from the top of the second column, "diagnosis of an early lesion" should be changed to "early diagnosis of a lesion."

Book Reviews

Medicine and the War. Edited by William H. Taliaferro, M.D. Price, $2. Pp. 193. Chicago: University of Chicago Press, 1944.

This series of ten lectures on "Medicine and the War," given by members of the faculty of the University of Chicago, were intended for student groups and are discussions of a series of medical problems highlighted by the war. The science and art of medicine play a most important role in modern warfare.

The first lecture by Dr. Arno B. Luckhardt is a historical review of the role of medicine in war. This is followed by a consideration of food as a basic fuel for both soldier and civilian in wartime. Another lecture reviews the recent advances in chemotherapy, especially the sulfonamide compounds, antimalarial agents, penicillin and thyrothricin. Dr. William H. Taliaferro's survey of the problem of malaria is excellent and indicates that malaria is the most important infectious disease in the present war. Dr. Clay G. Huff reviews the problems related to changes in modern transportation and how airplane travel can afford unwanted aid in the dissemination of diseases and disease-carrying insects. Dr. Alexander Brunschwig considers the problem of shock and blood substitutes. Aviation medicine is a new field of medicine, with its own physiologic and psychologic problems. The problems of anoxia, speed and acceleration and pilot fatigue and black-out make fascinating reading for the physician. Other lectures deal with the neurologic and psychologic effects of cerebral injuries, psychiatry and the war and chemical warfare.

These lectures stress the need for scientific research in development of better methods for saving life in war and emphasize the numerous ramifications of medicine in war. It is highly recommended as an important and timely contribution.

side opposite the line of fracture. In 39 cases there was no fracture of the skull. In 19 of these 39 cases death occurred in the absence of any injury except the cranial trauma. The authors conclude therefore that "the presence or absence of a fractured skull as a criterion of the severity of cerebral injury would seem to be a loose standard." Concomitant injuries were often masked by unconsciousness. They were held responsible for death in 7 of 94 cases of fracture of the skull and in 9 of the 39 cases in which no fracture was present.

The following clinicopathologic correlations were of interest: Of 10 cases in which a state of consciousness suggested a progressive lesion, a subdural or an epidural hemorrhage was the cause of death in 4; in 4 others a diffuse injury to the brain was present, and in 2 cases fatty cerebral embolism was the cause of death. In the great majority of cases with profound injury to the head no remarkable change in blood pressure and pulse was apparent throughout the period of hospitalization. In 13 the temperature was 105 to 109 F. at the time of death. Respirations were above 40 per minute in 21 cases. The most prominent and puzzling feature of the "neurogenic" pattern of death was tachypnea, with or without pulmonary edema.

SHENKIN, Philadelphia.

Treatment, Neurosurgery

FOLLOW-UP STUDIES OF A SERIES OF PATIENTS TREATED BY ELECTRICALLY INDUCED CONVULSIONS AND BY METRAZOL CONVULSIONS. B. L. PACELLA and S. E. BARRERA, Am. J. Psychiat. 99:513 (Jan.) 1943.

Pacella and Barrera studied 144 patients treated with electrically induced convulsions and 126 patients treated with metrazol. The therapeutic effects in the two groups were essentially the same, especially in patients with psychoses. The statistics are slightly in favor of electric shock. In view of this and the less undesirable effects with electrical shock, the authors believe that those of metrazol shock should be discontinued in favor of the employment of electric shock. They conclude that convulsive therapy is of great value for the affective psychoses, as compared with the results for schizophrenia. The best results were obtained in patients with depression, feelings of guilt, self depreciation and suicidal tendencies.

FORSTER, Philadelphia.

CONVULSIVE SHOCK THERAPY IN ELDERLY PATIENTS. VERNON L. EVANS, Am. J. Psychiat. 99:531 (Jan.) 1943.

Evans investigated the results and the risks entailed in convulsive shock therapy in a group of 50 patients over 50 years of age. Of this group, 21 recovered and 19 showed improvement. The results were considered comparable to those obtained in treatment of similar psychoses in younger patients. No patient was refused convulsive treatment because of physical risks alone. Two patients suffered fractures of the humerus, which healed uneventfully. One patient had pneumonia in the course of treatment and died, but this was considered incidental, and not the result of treatment. Evans concludes that the risk of administration of shock therapy to elderly patients is well worth taking.

FORSTER, Philadelphia.

THE ELECTROFIT IN THE TREATMENT OF MENTAL DISEASE. DAVID J. IMPASTATO and RENATO ALMANSI, J. Nerv. & Ment. Dis. 95:395 (Oct.) 1942.

Impastato and Almansi describe the essential features of the apparatus used in the production of the electric fit. They advocate the use of a constant time interval of one-tenth second and an increase of the voltage rather than of the time when a stronger stimulus is necessary. The authors believe that this minimizes the danger of cardiac accidents. The method may be used for patients with manic-depressive psychosis, schizophrenia, involutional psychosis and severe psychoneuroses, and possibly certain organic psychoses. Patients should be free from severe constitutional disease and may be up to 60 years of age. Treatments should be given with the patient in hyperextention, in which position the danger of fracture of the spine is almost nil. At the beginning of therapy the authors attempt to establish the individual convulsive threshold. They then increase the voltage sufficiently to produce a grand mal seizure. Two treatments a week are given until recovery, which is followed by one or two more treatments. The responses which may be obtained are classified as follows: (1) the conscious reaction, in which the patient does not lose consciousness; (2) a blank, characterized by fleeting unconsciousness and sudden flexor spasm; (3) petit mal. with a longer period of unconsciousness, more violent spasm and retrograde amnesia, and (4) grand mal, characterized by initial flexor spasm, a period of apnea, a tonic and a clonic phase, a second period of apnea and postconvulsive phenomena. For patients who thrash about after the attack 3½ grains (0.227 Gm.) of sodium amytal may be given intravenously. Electroencephalographic changes associated with the electric fit are identical with those associated with metrazol seizures except that the abnormal activity following the electric convulsion lasts a shorter time. The authors enumerate a number of advantages of the electric fit over the metrazol convulsion, one of the most important being the complete amnesia for the treatment, so that patients do not object to continuing treatment. Of 50 patients who completed treatment, 80 per cent in the manic-depressive group and 50 per cent in the schizophrenic group recovered or showed improvement. Fewer complications were seen with the electric shock method than with the metrazol method. Those noted were dislocations of the jaw, fracture of the fifth dorsal vertebra and, in 1 patient, severe pains in the muscles of the arm. Transient loss of memory, depersonalization and confusion may be expected during periods of treatment and are not of bad prognostic import. CHODOFF.

OBSERVATIONS ON THE KENNY TREATMENT OF POLIOMYELITIS. F. H. KRUSEN, Proc. Staff Meet., Mayo Clin. 17:449 (Aug. 12) 1942.

The Kenny concept of poliomyelitis is apparently in no conflict with the accepted proof of damage to the anterior horn cells and flaccid paralysis. It asserts, however, that early in the disease the major symptoms are not so much flaccid paralysis as "muscular spasm," "incoordination" and "mental alienation."

Krusen found that muscular spasm occurs during the early stages of poliomyelitis, that it may be widespread and that it is something more than the result of meningeal irritation, as was previously thought. The principal sites of such spasms are the hamstring muscles; the muscles of the back and neck; the gastrocnemius, pectoral, quadriceps and biceps muscles, and the muscles of respiration. The Minneapolis investigators of the Kenny concept define muscular spasm as a group of symptoms, including fibrillary twitchings (fasciculation), hyperirritability of the muscle to stretching and a more or less tonic state of contraction of the muscle fibers, which frequently cannot be overcome even by great force.

Incoordination is defined as "(1) that due to the spreading of motor impulses intended for a certain muscle to other muscles or groups of muscles due to

CONTENTS OF PREVIOUS NUMBER

SEPTEMBER 1944. NUMBER 3

ARCHIVES OF

NEUROLOGY AND PSYCHIATRY

OCTOBER 1944

TABLE 1.—Data on Ninety Patients with Head Injury*

Condition	Total No.	Unstable Personality Background			Severity of Injury					Electroencephalographic Ratings				Mean Time After Injury	Pneumoencephalographic Ratings					Rorschach Ratings				Situational Factors					
		0	1	2	0	1	2	3	4	0	1	2	3		0	1	2	3	4	Instability Mean ± Standard Error		Disability Mean ± Standard Error		None	Compensation (A)(B)	Military Service	Draft	Legal Factors	Individual Problems
Headache																													
Localized	22	18	3	0	2	8	6	2	3	6	4	3	4	1 yr. 5 mo.	0	1	2	3	1	14.7 ± 1.69		13.1 ± 1.65		3	5.5	5	1.5	0	3
Hemicranial	3	0	3	0	1	2	0	0	0	2	0	1	0	2 yr. 2 mo.	1	0	2	0	0	8.0 ± 1.73		3.7 ± 2.18		3	0	0	0	1	1
Occipital	11	0	1	1	5	2	2	1	1	3	1	1	1	1 yr. 6 mo.	0	1	2	1	0	13.9 ± 3.28		8.3 ± 2.20		3	1	0	0	1	1
Bilateral	13	1	5	2	4	2	4	1	2	7	2	4	0	1 yr. 8 mo.	0	0	2	1	0	18.7 ± 3.36		9.1 ± 1.69		1	5	2	0	1	2
Generalized	7	2	3	2	4	0	2	1	0	1	0	1	0	1 yr. 8 mo.	0	2	1	0	1	17.0 ± 3.14		11.5 ± 3.31		2	2.5	2	2.5	0	0
Bizarre	11	1	5	3	2	6	1	2	0	6	2	3	0	1 yr. 1 mo.	1	2	3	0	0	20.1 ± 3.06		4.6 ± 2.10		0	3	4	0	2	2
Other symptoms	9	1	5	0	4	3	3	0	0	6	1	1	0	1 yr. 3 mo.	0	0	0	0	0	15.2 ± 3.64		5.4 ± 2.18		2	3	2	0	0	0
Controls:																													
With some headache	8	2	5	1	2	1	2	1	1	3	2	2	0	1 yr.	0	0	0	1	0	15.0 ± 3.02		6.9 ± 1.31		7†	0	0	0	0	1
With no headache	11	8	3	0	3	1	1	1	0	5	3	3	0	1 yr.	0	0	1	0	0	16.0 ± 3.12		1.1 ± 2.09		7†	0	0	0	0	1
With evidence of organic defects	3	3	0	0	0	0	3	0	0	1	0	1	0	.... 6 mo.	0	0	1	0	0	18.0 ± 6.0		13.5 ± 5.50		2†	1	0	0	0	0
Total	90	43	30	14	25	27	20	9	9	41	16	16	7	1 yr. 1 mo.	1	6	11	11	2	16.0 ± 0.92		8.5 ± 0.81		25	19	15	4	4	15

* The figures in bold face are those which show a significant difference from the rest in the series.
† The significance for these figures was established by the combination of two or three groups.

be classified under either of one of two types, but most of the headaches are recognizable as conforming to one of the following patterns. 1. The pain of localized headache has its onset, or is maximal, in one area on one side of the head, with a variable amount of extension to the rest of that side of the head. The site of the pain is usually where the patient was struck, but it may be the region of a contrecoup injury. It is most frequently frontal or parietal. Some patients have almost constant pain, but most of them have intermittent bouts, varying from several a day to about one a month, usually brought on by fatigue or exertion, sometimes by damp weather, sometimes by emotional stress and frequently by stooping or sudden movements of the head, and usually relieved by rest. We have the impression that many headaches of this kind were continuous at first, when the pain was more severe, but became less frequent as recovery progressed. 2. It may be that the hemicranial type is at one end of the localized series and is a late development in some cases of that form, for our patients with hemicranial headache were seen, on an average, longer after the injury than were the patients with the localized type. The hemicranial headache was of sudden onset, lasted several hours to two or three days and occurred from once a week to once a month, on the whole resembling migraine headache. 3. Occipital or suboccipital headache is bilateral and is sometimes accompanied by tenderness at the attachment of the posterior muscles of the neck, as though due to tension in these muscles. Occipital headache may be accompanied by the frontal type, thus shading over into the next form. 4. Bilateral headache may be frontal, temporal or parietal. There may be generalized extension, but the patient describes the maximal pain or the onset of the attack as in corresponding areas on the two sides of the head. 5. In generalized headache the pain is "all over" the head, and there is no localization. 6. The bizarre type includes the feeling of pressure over the vertex, the sensation of a "tight band" around the head and the pain which wanders from one part of the head to another, either according to the patient's presenting description or as reported on different occasions. Sometimes what has been superficially reported as a "headache" has resolved itself on closer questioning into a "crackling" feeling in the head or some other bizarre sensation and we have classified it under this head.

The incidence of these types of headache in our series is shown in table 1, which also includes data on patients presenting chiefly symptoms other than headache and on three small

HEAD INJURY
A STUDY OF PATIENTS WITH CHRONIC POST-TRAUMATIC COMPLAINTS

MAJOR W. D. ROSS
ROYAL CANADIAN ARMY MEDICAL CORPS
AND
F. L. McNAUGHTON, M.D.
MONTREAL, CANADA

The resemblance from case to case of certain sequelae to injuries of the head has led to a tendency to group these symptoms together in syndromes and to forget the patient behind them. These syndromes have been variously labeled—postconcussion syndrome, postcontusional state, post-traumatic meningeal headache, post-traumatic circulatory instability and traumatic neurosis—according to the inferred cause, and various rules of thumb have been suggested for their handling. In actual fact, there is no such thing as "post-traumatic headache" in the abstract. There are only individual patients complaining after injury to the head of headache, dizziness, fatigue, irritability, "nervousness," impaired efficiency or other mental symptoms. In view of the fact that few complaints other than these could be made by a person who finds himself in an unsatisfactory situation after such an injury, it is evident that a superficial uniformity of symptoms may cover a variety of physical disorders and disturbances in personality. We report here the study, by both physical and psychologic methods, of a series of patients with such complaints, in an effort to sort out the various factors which are associated with them. A thorough review of the literature up to 1942 has been presented by Denny-Brown.[1] We shall refer to only a few of the recent observations elsewhere, together with the data obtained from the study of patients in this clinic. physiologic, psychologic and, in some cases, neurosurgical means [2] on 90 subjects several months or longer after an injury to the head, the series including 15 patients studied at repeated intervals during recovery from such injury, and the results of a follow-up inquiry into the effects of subdural insufflation and other methods which were used in this institute in the treatment of 82 other patients with post-traumatic headache or dizziness. The 90 subjects included patients, both civilian and military, with and without compensation claims, who were referred because of their symptoms, and several control patients, some with symptoms and some without, who returned for study at our request at a time after the injury comparable to that for the patients, but who would not otherwise have sought medical care.

The data on these 90 subjects are summarized in table 1, of which the main body of this paper is an explanation, under the following headings: (1) types of headache and controls, (2) previous personality background, (3) severity of injury, (4) electroencephalographic and pneumoencephalographic ratings, (5) results of the Rorschach test, (6) situational factors and (7) summary of significant associations and trends. The data on the series of 82 patients given insufflation treatments are presented in section 8. We shall also discuss (9) the vascular responses to posture, and, finally, we shall present a concept of (10) mechanisms, with implications for management.

MATERIAL AND METHODS

The material on which our data are based includes the results of direct studies by neurologic, psychiatric,

I. TYPES OF HEADACHE AND CONTROLS

In spite of the superficial uniformity of complaints already mentioned, it has been our experience that a careful inquiry into to what the patient means by his complaint, such as headache or dizziness, will give a valuable lead to the solution of the problem. The kind of headache has been particularly useful in this respect and has provided a basis for classification into several types. The relative importance of physical and psychologic factors in the various types will be discussed later.

The following types of headache are described: (1) localized, (2) hemicranial, (3) occipital, (4) bilateral, (5) generalized and (6) bizarre. There is shading between these types, and some patients will describe a headache which might

The other patients tended to have personality backgrounds similar to those of the psychoneurotic patients.

3. SEVERITY OF INJURY

Each patient was rated with regard to severity of injury on a scale of 0 to 4. Criteria for this rating included the duration of post-traumatic amnesia, which has been considered as the greatest single prognostic criterion in cases of head injury [5] and, when the patient had been under observation in a hospital, as had been the case with the majority of patients with severe injuries, the amount of blood in the spinal fluid, the presence of fracture of the skull and the presence of neurologic signs.

A rating of 0, or negligible injury, indicated loss of consciousness for less than ten minutes and absence of fracture. A rating of 1 indicated either post-traumatic amnesia for ten to thirty minutes or the presence of fracture of the skull or of from 100 to 1,000 red cells per cubic millimeter in the spinal fluid. A rating of 2 indicated the presence of any two of the following features: Post-traumatic amnesia for one to three hours; fracture of the skull; 1,000 to 20,000 red cells per cubic millimeter in the spinal fluid, and slight neurologic signs. A rating of 3 indicated post-traumatic amnesia of from three to forty-eight hours' duration and fracture of the skull, a red blood cell count up to 100,000 per cubic millimeter or pronounced neurologic signs. A rating of 4, or very severe injury, indicated the presence of three of the following features: post-traumatic amnesia of over forty-eight hours, fracture of the skull, a red cell count of over 100,000 per cubic millimeter of spinal fluid and pronounced neurologic signs.

These criteria are described only as approximations, for they were essentially clinical ratings, which took into consideration possible distortions of the post-traumatic amnesia and discrepancies in various sources of information and other relevant data. They are given not as representing sharp lines of differentiation in the degrees of injury but as indicating roughly the severity of injury.

In table 1 the number of patients with each rating is charted in relation to each type of headache and each control group. It will be seen that the patients with organic defects and those with localized headache tended to have relatively more severe injuries, while patients with hemicranial headache, generalized and bizarre headache and symptoms other than headache tended to have less severe injuries.

4. ELECTROENCEPHALOGRAPHIC AND PNEUMOENCEPHALOGRAPHIC RATINGS

The next sections of table 1 present ratings for electroencephalographic and pneumoencephalographic abnormalities. For 80 patients we had the results of electroencephalographic examination at some time between three months and four years after injury or else a normal electroencephalogram made in less than three months after the accident, indicating that the pattern was still normal within this period. The mean time after injury at which the electroencephalographic study was made on each group is indicated in the table. For 31 of these patients we also had pneumoencephalographic studies. For comparison of the results of these methods of study with the other data, we had them rated independently of the clinical information. Dr. Jasper rated the electroencephalographic abnormalities on a 4 point scale. Dr. Childe rated the roentgenographic evidence, using a score of 0 to 3 for degrees of ventricular dilatation and a score of 0 to 2 for degrees of widening of the sulci. These two scores were added to give a 5 point rating, though no patient achieved such a score.

The relation of these ratings to the type of headache will be considered in section 7 of this paper.

As in the series reported by Williams,[6] about one-half our patients with chronic symptoms showed electroencephalographic abnormalities. However, the ratio was found to be the same for our control patients as for the patients who complained of symptoms.

Both the electroencephalographic and the pneumoencephalographic ratings showed a slight correlation with the severity of the injury: 0.264 ± 0.085 for 53 electroencephalographic ratings made between three months and two years after the injury and 0.383 ± 0.102 for 31 pneumoencephalographic ratings. We were not able to show a significant correlation between the electroencephalographic ratings obtained over two years after the injury and the severity of the injury, or between the electroencephalographic and the pneumoencephalographic ratings. However, no patients had a report of electroencephalographic abnormality which was not substantiated by pneumoencephalographic evidence when this was obtained also. In table 2

5. Jefferson, G.; Cairns, H.; Brain, W. R., and Guttmann, L., in Discussion on Rehabilitation After Injuries to the Central Nervous System, Proc. Roy. Soc. Med. **35**:295-308 (Feb.) 1942.

6. Williams, D.: The Electroencephalogram in Chronic Posttraumatic States, J. Neurol. & Psychiat. **4**:131-146 (April) 1941.

control groups. The control patients with headache were those who returned at our request, and not because of their symptoms, but who had had some headache since their injury. The figures for these patients have been included in the distribution according to the type of headache; so these figures are not included in the totals at the foot of the table. Of this small group of 22 patients whom we were able to bring back for study, 8 had had headaches but carried on with their work, 3 had evidence of frank "organic" effects of the injury and only 11 had been completely free from headaches or other symptoms after a reasonable period of convalescence. It was difficult to get a larger number of symptom-free controls among persons with former head injuries, as many either had moved away on military duty or, because of their freedom from symptoms, were not sufficiently interested to cooperate.

The relation of the other evidence to the type of headache will be considered after we have explained how each kind of evidence was obtained.

2. THE PREVIOUS PERSONALITY BACKGROUND

As an assessment of the previous stability of the patients and the controls during childhood and up to the time of the accident, we employed a psychiatric interview planned to obtain certain comparable data. This was based on the kind of data reported as frequently obtained from soldiers who failed to return to duty after a neurotic illness [3] and from many persons exhibiting neurotic reactions in wartime.[4] The points covered in every interview were as follows: (1) family history of nervous or mental disease, including neurosis, alcoholism and "sick headache"; (2) history of a broken home before midadolescence, death of a parent or divorce of, or serious quarreling between, parents; (3) previous history of nervous symptoms or emotional breakdown or of a psychosomatic disorder occurring in relation to stress; (4) presence of childhood fears, such as fear of the dark, requiring a night light, or night terrors; (5) enuresis after the age of 6 years; (6) nail biting after the age of 10; (7) tics of more than brief duration; (8) stammering; (9) sleep walking on more than three occasions; (10) poor school record, truancy or attainment of a grade two years over the average age; (11) avoidance of fights as a boy; (12) avoidance of dangerous games; (13) excessive reaction to interests, wakefulness at night before an exciting event, going off food for two or three meals, slight diarrhea or exhaustion after such an event; (14) light, restless sleep; (15) fainting at the sight of blood; (16) a hypochondriacal attitude, including total abstinence from drinking and smoking if for reasons of health; (17) poor work history, frequent changes in jobs or dissatisfied attitude toward work, and (18), if the patient was in one of the services, inadequate motivation, such as reasons other than a desire to fight or to do his part.

It is realized that these items include a mixture of factors predisposing to instability and of actual symptoms of neurosis and that there is only empiric justification for their being presented together. However, they have proved useful even in this unanalyzed way, without any attempt to determine their relative value and significance. Although their significance in any particular case must be considered in the light of clinical judgment, we believed that a more objective rating was possible if these points were used in a purely quantitative way.

The ratings for an unstable personality background, shown in table 1, were obtained by scoring 0 if none to two of the aforementioned eighteen items were present; 1, if three to four items were present, and 2, if five or more items were positive. Avoidance of fights and dangerous games was not counted in the rating for female patients. The numbers in the table opposite each type of headache and each group of controls represent the number of patients presenting each rating. It will be noted that the totals under "unstable personality background" do not quite reach 90. This discrepancy is present to varying degrees for the different types of evidence because, for one reason and another, every type of evidence could not be obtained for every subject studied.

Eight psychoneurotic patients, without head injury, were also studied according to the same plan of interview and by the same examiner who interviewed all the patients data on whom are recorded in table 1. Of these patients, 5 gave ratings of 2, for the item under discussion, and 3, ratings of 1. These subjects are too few to provide an adequate group of psychoneurotic controls, but similar data have frequently been reported in the histories of neurotic patients. It will be seen from the table that the controls with no headache, the controls with organic defects as a result of the accident and the patients with localized headache were low in evidence of a previous unstable personality background.

3. Lewis, A., and Slater, E.: Neurosis in Soldiers: Follow-Up Study, Lancet **1**:496-498 (April 25) 1942.

4. Gillespie, R. D.: Psychological Effects of War on Citizen and Soldier, New York, W. W. Norton & Company, Inc., 1942, p. 251.

but it revealed striking changes in relation to head injury which were not brought out by the span of digits test except in cases of extreme injury.

Table three shows that within three weeks of a severe injury to the head (3 to 4 on our scale) the "disability" rating was notably raised, while with only slight or moderate injury (0 to 2) it was not raised more than to the mean for neurotic patients while the "instability" rating was raised almost to the mean for such patients.

For patients more than one month after head injury the mean for the "disability" rating was

ity of the injury and the stage of recovery from injury. "Instability" ratings also tended to be higher with electroencephalographic and other evidence of changes in the brain, although the "disability" rating was about the same one month after injury in groups divided on the basis of this evidence.

The changes with recovery from injury, as determined by repeated examinations on the same patients, are shown in table 5. Patients with severe injuries showed high "disability" ratings, which manifested recovery with time, although for 1 patient (E. G.) there was no improvement in the "disability" ratings, and

TABLE 3.—*Incidence of Rorschach Ratings*

	Number of Patients	Instability		Disability	
		Mean	Standard Error	Mean	Standard Error
Psychoneurotic patients	50	17.9	± 1.53	8.4	± 1.3
Patients with "organic" disease of brain........................	24	8.75	± 2.42	25.1	± 2.69
Healthy persons of superior intelligence.........................	50	3.6	± 0.66	1.1	± 0.75
Royal Canadian Army Medical Corps, 1940.......................	50	14.1	± 1.20	7.6	± 1.06
Patients with post-traumatic headache					
Tests within 3 weeks of head injury:					
Slight or no evidence of cerebral damage (0-2).............	10	16.4	± 2.85	7.3	± 2.92
Marked evidence of cerebral damage (3-4).................	10	7.4	± 2.89	30.7	± 4.43
Test more than 1 month after head injury:					
Without neurotic background.............................	43	12.1	± 1.24	9.2	± 1.61
With neurotic background................................	44	18.4	± 1.61	8.0	± 1.34
With seizures	11	18.7	± 3.05	16.8	± 3.51

about that for neurotic patients, regardless of the personality background, while the "instability" rating was significantly higher in the presence of evidence of a neurotic personality background (rating of 1 or 2 on our scale for previous personality background) than in its absence (rating of 0). No other item, such as severity of injury, time after injury, presence of an electroencephalographic abnormality or a clinical judgment of cerebral damage based on an accumulation of the various types of evidence, showed a significant correlation in the entire series of patients with cerebral injury more than one month after the accident.

When only the 43 patients among those without a background of previous unstable personality were studied for correlation with "instability" and "disability" ratings, certain suggestive trends were present, as indicated in table 4. These trends might prove significant in a larger number of patients: a slightly greater tendency to "disability" with severe injuries than with moderate injuries, and to its appearance within a period of two years than after two years, and an even greater tendency to "instability" with these two factors, i. e., the sever-

TABLE 4.—*Nonsignificant Trends in Rorschach Ratings for Forty-Three Patients Without Previous Neurotic Background*

Rorschach Rating	Severity of Injury		Time After Injury		Electroencephalographic Abnormality		Evidence of Organic Changes		
	Moderate	Severe	Under 2 Yr.	Over 2 Yr.	Present	Absent	Absent	Moderate	Pronounced
Instability........	12.1	17.0	14.3	11.0	14.0	16.1	13.5	15.0	19.0
Disability.........	9.6	11.8	10.1	8.3	8.7	8.1	10.0	8.6	9.2

this patient continued to show clinical evidence of severe "organic" intellectual impairment. The "instability" ratings for the patients with severe injury, however, tended to rise with improvement in the "disability" ratings. The case of E. T. is particularly interesting. Of previously stable personality, this man had a severe contusion and during convalescence passed through a phase with symptoms of irritability and dizziness, recovering spontaneously in about nine months. In relation to this clinical situ-

the patients with a high pneumoencephalographic rating and a low or negative electroencephalographic rating were those tested two years or more after the injury, when the electroencephalographic abnormality had diminished but the pneumoencephalographic abnormality remained. If the results of both procedures had been determined for more patients from six months to one year after injury, a significant positive correlation might have been demonstrable.

The demonstration in table 2 that the electroencephalographic ratings were usually more conservative than the pneumoencephalographic ratings, together with the relatively greater convenience of the electroencephalographic procedure than of the pneumoencephalographic method, indicates a considerable degree of usefulness for the electroencephalogram in the assessment of the status of patients with complaints after head injury, at least less than two years after the injury. When, however, there are medicolegal considerations or the question is one of com-

TABLE 2.—*Numbers of Cases in Relation to "Organic" Ratings*

		Pneumoencephalographic Rating					
		0	1	2	3	4	Totals
Electroencephalographic rating	0	1	1	3	2	2	9
	1	0	2	2	4	0	8
	2	0	1	3	4	0	8
	3	0	1	2	2	0	5
	4	0	0	1	0	0	1
Totals		1	5	11	12	2	31

pensation or pension, neither the electroencephalographic nor the roentgenographic evidence should be used without the severity of the injury and the constitution of the patient prior to the injury being considered. Either method might reflect not only the effects of the injury itself but a cerebral abnormality antedating the accident.

5. RESULTS OF THE RORSCHACH TEST

Psychologic tests used in this study included the Binet and Snedden word lists,[7] the repetition of digits, the Kraepelin continuous subtraction test[8] and the Shipley-Hartford retreat test,[9] as well as the Rorschach method. The word lists did not differentiate the clinical types. Subjects

without headache and patients with various types of headache showed mean verbal intelligence levels corresponding with intelligence quotients of about 100. The span of digits and the continuous subtraction test gave poor results with evidence of severe damage to the brain or of severe neurosis but did not appear to differentiate between the two conditions. The Shipley-Hartford test has been used to indicate the presence of subdural hematoma,[10] but it apparently does not measure lesser degrees of "organic" impairment, for its results in our series showed no relation to severity of the injury or to electroencephalographic or pneumoencephalographic evidence of cerebral damage except in cases of extreme injury.

The Rorschach method, on the other hand, gave striking results in a comparison of patients with head injury and patients with other disturbances, as well as when the test was repeated at intervals during recovery from the head injury. We administered and scored the Rorschach test according to the instructions of Klopfer and Kelley[11] except that the "testing of the limits" was omitted in order to avoid invalidation of repetitive tests during the course of recovery. From the Rorschach scores obtained in this standardized manner certain derivatives were obtained, as described elsewhere in detail.[12] These were the ratings for "instability," which were high for psychoneurotic patients, and of "disability," which were high for patients with cerebral disease. In table 3 are reviewed the levels of these ratings for various groups of subjects, including those with post-traumatic headache, psychoneurotic patients, with tumor of or damage to the brain and two groups of controls, one of superior intelligence, with a probable mean intelligence quotient of over 120, and one of low average intelligence, with a probable mean intelligence quotient of about 90. The rating for "instability" was related not only to neurotic trends but to intelligence. It showed a negative correlation with the Binet word list (— 0.51 ± 0.069), but it differentiated two groups of subjects differing in evidence of neurotic background, although the Binet word list does not do so. The "disability" rating showed a negative correlation (— 0.46 ± 0.074) with the span of digits test,

7. Snedden, D. S.: A Study in Disguised Intelligence Tests, Contributions to Education no. 291, New York, Columbia University Teacher's College, 1927.

8. Sherman, I. C.: Study of Kraepelin's Continuous-Subtraction Test, J. Abnorm. Psychol. 18:385-388 (Jan.-March) 1924.

9. Shipley, W. C., and Burlingame, C. C.: Convenient Self-Administering Scale for Measuring Intellectual Impairment in Psychotics, Am. J. Psychiat. 97:1313-1325 (May) 1941.

10. Abbott, W. D.; Due, F. O., and Nosik, W. A.: Subdural Hematoma and Effusion as Result of Blast Injuries, J. A. M. A. 121:739-741 (March 6) 1943.

11. Klopfer, B., and Kelley, D. M.: The Rorschach Technique, Yonkers, N. Y., World Book Company, 1942, p. 448.

12. Ross, W. D., and Ross, S.: Some Rorschach Ratings of Clinical Value, Rorschach Research Exchange 8:1 (Jan.) 1944.

eral factors, i. e., eligibility for compensation and draft into the army, were given halfscores in each of the pertinent columns.

The individual personal difficulties which were discovered involved a wide variety of human hopes and fears. One man had had a marriage proposal spurned by the one woman he had ever dared to take out, and this occurred just previous to his accident. One woman had pent-up resentment against her husband for taking in boarders, which involved more work for her. She acquired a headache which she blamed on a minor injury six months previously, for which her husband had been accidentally responsible. Another woman was worried about her relatives in Russia. These situations were probably only contributory to more basic personality difficulties, but a full understanding of each case appeared to involve the relation of the previous personality background, the effects of the accident and the life situation after the accident.

It will be seen in table 1 that individual problems alone rank third among the situational factors presented by the patients, with Workmen's Compensation payments coming first and service of a military nature second. The differences between the patients and the controls and between various groups of patients will be discussed in section 7. This situational factor must, of course, always be interpreted in relation to the whole physical and personal condition of the patient, but by treating it as a statistical item, sought in both patients and controls, we have hoped to avoid the subjective biases of interpretation.

7. SIGNIFICANT ASSOCIATIONS AND TRENDS

On the basis of table 1, comparisons can be made both of the patients and the control subjects and of the patients with various types of headache and the three types of control subjects.

After the data for the 8 control patients who had some headache but did not present themselves because of their symptoms are removed from the total body of data for patients presenting headaches of various types and from the data for patients with other symptoms, we may compare the results for the 68 patients seeking medical care for symptoms after head injury and our control group of 22 persons who returned for study at our request. The only types of evidence which differ significantly in these two main groups are the severity of injury and the situational factors.

The evidence for severity of injury is significantly greater ($X^2 = 3.95$) for the control subjects than for the patients. There are two reasons for this. Our control subjects included

3 with very severe injuries and persisting neurologic defects who were selected purposely to provide at least a small control group representing severe trauma. In addition, almost all our control patients were persons whose injury had been of sufficient severity to warrant admission to the Montreal Neurological Institute, whereas a fair proportion of the patients had not been hospitalized at the time of their injury. The only importance of this difference to us is that it illustrates that the control group did not, at any rate, suffer less trauma than did the patients.

It appears of greater importance, however, that, whereas the patients and the controls did not differ significantly with respect to previous personality background, electroencephalographic patterns or Rorschach ratings, they did differ strikingly in the incidence of discoverable situational factors. All the control subjects taken together had a low rating ($X^2 = 29.7$, which

TABLE 6.—*Age Distribution of Patients Admitted to the Montreal Neurological Institute from 1938 to 1942*

Complaint	Below 18 Yr.	18-50 Yr. of Age	Over 50 Yr.
Post-traumatic headache..........	6	91	10
Acute head injuries................	257	374	126

is highly significant) for these factors as compared with the patients who sought medical care. Although we aimed at an unselected control group with regard to these factors, this difference may be exaggerated because of the difficulty of getting controls to return who were in the armed forces or were busy in war industry. Again, there might be some distortion as a result of a greater willingness of the patients seeking help to discuss their problems. Nevertheless, this difference does suggest that the complaint of post-traumatic symptoms is often related to the patient's life situation, although he might have symptoms without complaining of them if his situation is satisfactory or if there is no gain in complaining. This is in accord with Brain's [5] report of a greater frequency of complaints among patients after industrial accidents than among those after road accidents.

In this connection it is of interest that post-traumatic headache and dizziness are rare complaints in children. In the few cases we have encountered the complaint was made by the mother, and the connection of the headache with the injury was extremely dubious. At Dr. Cone's suggestion, we sought evidence on the

ation, table 5 reveals a falling "disability" rating with a rising "instability" rating, which reached a neurotic level while he had these symptoms and returned to normal when he was "himself" again. There was no compensation factor in this case.

The patients with less severe injury showed less evidence of "disability" and more immediate elevation of the "instability" rating, followed by a subsequent fall in some cases, but not in others.

Although it is necessary to make interpolations in the far from complete evidence which we have obtained, it appears that head injuries are followed by features detectable by the Rorschach method, at first of a variable degree of "disability," similar to that associated with cerebral disease and then by a degree of "instability"

6. SITUATIONAL FACTORS

Each patient was considered for the presence of factors in his life situation at the time of or after the accident which might have contributed to the presence or aggravation of symptoms by providing either a mental conflict producing tension or a secondary gain to be obtained as a result of symptoms. The distributions of the situational factors has been summarized in the last section of table 1 according to each type of headache and the types of control.

The columns in this section of the table may be summarized as follows: 1. Apparently, no contributing situational factors.

2. Workmen's Compensation payments. This column was divided into (*A*) factors not appearing to contribute to the symptoms, according to our understanding of the case, and (*B*)

TABLE 5.—*Serial Rorschach Ratings Following Injury to the Head for Fifteen Patients**

	Instability						Disability					
	Less Than 2 Wk.	2 Wk.-1 Mo.	1-6 Mo.	7 Mo.-1 Yr.	1-2 Yr.	Over 2 Yr.	Less Than 2 Wk.	2 Wk.-1 Mo.	1-6 Mo.	7 Mo.-1 Yr.	1-2 Yr.	Over 2 Yr.
After severe injury:												
E. T.	11	17	..	7	..	..	41	21	..	4	..	..
J. R.	0	..	..	20	..	..	13	..	..	0	..	..
A. D.	..	0	-8	22	..	..	..	34	27	17	..	..
B. M.	6	13	..	..	..	..	42	— 9	..	..	..	..
E. G.	..	— 1	0	7	..	..	..	49	41	45	..	..
J. D.	..	..	11	..	24	..	..	..	31	..	17	..
J. T.	..	..	..	21	..	18	..	..	..	9	..	— 1
H. M.	..	..	..	33	36	..	..	..	..	10	6	..
F. P.	..	..	..	..	8	21	..	..	..	..	36	19
After minor to moderate injury												
L. K.	17	29	..	..	..	..	30	13	..	..	..	..
D. L.	26	17	15	..	..	..	7	10	2	..	..	..
D. W.	26	..	..	18	..	..	7	..	..	— 1	..	..
L. R.	24	..	..	39	..	..	2	..	..	— 1	..	..
R. R.	4	..	2	..	..	..	— 3	..	2	..	..	..
A. K.	..	..	..	..	8	10	..	..	..	..	2	2

* Periods indicated in the column heads are those at which the ratings were determined.

similar to that for psychoneurotic patients. The degree of "instability" may be related slightly to the severity of injury and the amount of cerebral damage, but it is much more closely related to the previous personality background. It appears that "the fault, dear Brutus, is not in our stars, but in ourselves!" Whether the increased "instability" is a direct result of cerebral trauma, or whether it has an indirect cause, in the personal problems encountered by the victim of such trauma, we do not think our evidence is sufficient to show. We hope that either Nature or the hand of war will yet provide us with a subject or subjects on whom a Rorschach test has been made *before* head injury, with an opportunity to repeat such tests at intervals during recovery!

The relation of the "instability" and "disability" scores to the type of headache will be considered in section 7.

factors appearing to play a part, at least in the aggravation of complaints.

3. Military services, in the Army, Navy, Air Force or Merchant Marine, which presented a mixed situation of unpleasant duties and probable danger, and in the first three services, possible pension.

4. Draft. The patients were facing a call for military training.

5. Legal factors. A lawsuit concerning the accident was pending.

6. Individual problems. Although none of the general situations often associated with accidents were present, an individual problem might be related to the symptoms.

Many of the patients with situational factors related to compensation and service also had personal problems, but the cases were tabulated in the column only for the general factor. Two patients whose cases involved two of the gen-

ventricles on pneumoencephalographic study in spite of a mild or doubtfully severe head injury, and it is questionable whether such a change may not indicate a constitutionally defective nervous system rather than the results of trauma. The condition of these patients has impressed us as resembling hysteria in that secondary gain, rather than anxiety, was important. The generalized and bilateral headaches tended to approach the bizarre type in many characteristics, while the occipital form tended to be intermediate between these and the localized headache and presented more definite evidence of anxiety and tension.

The patients with hemicranial headache seem to form a special group. They rated low with respect to severity of injury, electroencephalographic changes and Rorschach "instability" and

intermediate ratings for most other characteristics. It is interesting, also, that, of the controls, those with headache tended to have higher ratings for unstable personality than those without headache, although they were not higher in Rorschach "instability" rating.

We believe, then, that these trends allow us to place some weight on the description of headache presented by the patient with respect to the relative importance of physical and psychologic factors in the production of the headache, although we agree with Denny-Brown [1] and with Symonds and Lewis [14a] that "physiogenic" and "psychogenic" features can never be completely dissociated in the living patient. Whatever the physiologic mechanism of the symptoms, an inverse relation between the previous stability of the personality and the evidence for physical and

TABLE 7.—*Data on Follow-Up Study of Treatment of Eighty-Two Patients with Post-Traumatic Symptoms*

	Total Number of Operations	Effect on Headache				Improvement with Relapse to:			Effect on Dizziness				Improvement with Relapse to:		
		No Change	Slight Improvement	Considerable Improvement	Cure	Considerable Improvement	Slight Improvement	Same Condition as Before	No Change	Slight Improvement	Considerable Improvement	Cure	Considerable Improvement	Slight Improvement	Same Condition as Before
Spinal insufflation	40	16	6	1	4	5	1	7	14	2	0	4	0	1	1
Cranial insufflation	35	3	5	3	4	2	3 ·	15	6	5	2	1	3	0	8
Encephalographic study	21	11	0	2	2	3	0	3	7	0	1	2	1	0	1
Direct surgical measures	8	0	0	3	3	0	0	2	1	1	0	2	0	0	1
Totals	104	31	11	9	13	10	4	27	28	8	3	9	4	1	11

"disability" ratings. In view of the fact that these were patients seen on an average longer after injury than the patients with localized headache, their headache might represent a later and milder form of the latter. On the other hand, all 3 patients showed moderate evidence of previously unstable personality background, in spite of fairly high intelligence quotients and good Rorschach ratings. It may be that their headache was akin to migraine, with which there is often an unstable background, together with a superior intellectual level. These patients, in common with patients with migraine, were also helped by the administration of ergotamine tartrate. At any rate, this type of headache is not frequent and tends to undergo spontaneous improvement.

The patients without headache but with other symptoms, such as dizziness, fainting spells, irritability, "nervousness" and fatigue, had high ratings for previously unstable personality and

situational factors was striking. Most of the cases could be understood in terms of the constitution of the patient prior to the injury, its modification by the injury and the situation with which the person was faced. Hence, although further light on the physiologic mechanisms of post-traumatic symptoms would be useful in the management of the patients, we cannot get away from the need to consider each patient as a whole.

8. REEVALUATION OF THE SUBDURAL INSUFFLATION TREATMENT

A summary of our follow-up study on 82 patients who had previously been treated in this institute for post-traumatic headache or dizziness is presented in table 7. It includes the data on patients for whom we have been able to obtain follow-up information from six months to eight years after a spinal or a cranial subdural insufflation, as compared with the evidence for a control series for whom only a diagnostic en-

frequency of post-traumatic headache as compared with the incidence of head injuries in children. This is presented in table 6 on the basis of the number of admissions of patients of different age groups to the Montreal Neurological Institute over a five year period. The ratio of the incidence of patients with post-traumatic headache to patients with head injury is significantly greater in the 18 to 50 year old group than in the group under 18 years of age ($X^2 = 43.4$).

Of the figures for patients with the different types of headache and for the controls, given in table 1, those which differ significantly from the rest of the series are in bold face, or are marked with a dagger when the significance is established by the combination of two or three groups. They may be summarized as follows: The ratings for unstable personality background are low for patients with localized headaches ($X^2 = 11.4$) and for controls without headache ($X^2 = 4.3$) and are high for patients with generalized and bizarre headaches taken together ($X^2 = 10.08$) and for patients with symptoms other than headache ($X^2 = 5.74$); the ratings for severity of injury were high for controls with organic defects ($X^2 = 7.4$); electroencephalographic ratings were high for patients with localized headaches ($X^2 = 10.02$) and for controls with organic defects ($X^2 = 8.89$), and the Rorschach "disability" ratings were high for patients with localized headache ($t = 2.5$) and low for patients with hemicranial headache ($t = 2.7$).

Apart from these statistically significant associations between each condition and each type of evidence, there are trends in the various types of evidence which corroborate each other and which suggest that in a greater number of cases further associations could be established.

The patients with localized headaches not only had low ratings for an unstable personality background and high electroencephalographic and Rorschach "disability" ratings, but tended to have high ratings for the severity of injury and the pneumoencephalographic changes and somewhat low ratings for Rorschach "instability" as compared with patients with other types of headache. This much of the evidence tends to substantiate Penfield's [13] criticism of "an unmerited diagnosis of traumatic neurosis" for patients with localized headache, which he described as indicating a meningeal mechanism. With respect to situational factors, however, the patients with

localized headaches tended actually to rate higher than the other groups, if one includes all patients with compensation claims in order to avoid a bias in deciding when the compensation factor is relevant. This difference is not significant statistically, but it indicates that even the localized headache is not uninfluenced by the life situation of the sufferer. This fact may account for the inability of some authors [14] to separate patients with localized headache from patients with other types of headache which are influenced by personal factors. Patients with localized headache appear prior to injury to have been of a type superior to the patients in the other groups, to have suffered a more severe injury, to have more persisting electroencephalographic and pneumoencephalographic changes, to have lower Rorschach "instability" ratings but higher "disability" ratings, at least within several months of the injury, and to share with the other patients a relation of their symptoms to their personal setting.

The following case. is representative of this group of patients: W. M., a 26 year old corporal in the Royal Canadian Air Force, had been admitted to the Montreal Neurological Institute in 1941 for a localized headache, which had appeared one and a half years after a severe injury to the head (graded 3). Spinal subarachnoid insufflation of air was done .at that time, with the idea that the pain was due to subdural adhesions. When the patient was observed two years later, it was ascertained that he had been "cured" by the insufflation but that the headache had been related to a difficult personality situation, in which he worked long hours under an unsympathetic taskmaster. The patient, now a sergeant and doing well in his work, felt that a transfer to another station had been responsible for the improvement. He had had one or two bouts of headache since the treatment, in relation to fatigue and worry, which one would not expect if the basis of the headache had been stretching of adhesions by the insufflation. He did not give evidence of a previously unstable personality, and four years after the injury, when the effects of cerebral trauma were probably well resolved, the electroencephalogram was normal and he had low Rorschach ratings for both "instability" (+4) and "disability" (+1) and a high intelligence quotient (over 120). There was no pneumoencephalogram, as the. air had been directed to the subarachnoid space in 1941, and air studies were not repeated in 1943, when he was free from symptoms.

In contrast to the patients with localized headaches, the patients with bizarre headache tended to rate highest with respect to a previously unstable personality and Rorschach "instability" and lowest with respect to severity of injury, electroencephalographic changes and Rorschach "disability" rating. Some of them showed large

13. Penfield, W.: Chronic Meningeal (Posttraumatic) Headache and Its Specific Treatment by Lumbar Air Insufflation: Encephalography, Surg., Gynec. & Obst. 45:747-759 (Dec.) 1927.

14. (a) Symonds, C. P., and Lewis, A., in Discussion of Differential Diagnosis and Treatment of Post-Contusional States, Proc. Roy. Soc. Med. 35:601-614 (July) 1942. (b) Denny-Brown.[1]

considerably improved or had recurred, with considerable improvement nevertheless, was no better in the group subjected to spinal insufflation (10 out of 40) or in the group with cranial insufflation (9 out of 35) than in the group with pneumo-encephalographic therapy (7 out of 21), a treatment not considered specific for post-traumatic headache. This suggests that factors other than the insufflation may determine the result. There may have been patients, especially among those from whom we did not receive follow-up replies, whose headache was specifically affected by the insufflation treatment. A simultaneous psychiatric study of such patients would be required to establish the responsibility for cure, and we are unable to report any cases in which a long term cure was effected and other factors were definitely ruled out.

We tried to correlate the failures of spinal insufflation with failure to get air into the subdural space. However, in 2 of the patients who were cured the air entered the ventricles and not the subdural space, and in a considerable number of the patients who were not relieved of headache the air was in the subdural space. All the procedures were carried out by competent members of the attending or the house staff, presumably in accordance with instructions designed to insure a successful result. The fact that in a number of cases the air did not reach the subdural space may mean that this result is even more difficult to achieve than has formerly been thought.

The results of direct operation in the few carefully selected patients subjected to such a procedure seemed somewhat more specific, although this method of treatment of course carried more risk than the insufflation. In 2 patients the operation involved the cutting of adhesions when traction produced at operation, with the use of a local anesthetic, had reproduced the patient's pain. One of these patients, the cause of whose headache may not have been traumatic, has been under observation ten months, with no return of headache. The other patient showed temporary improvement but had a relapse within six months. One patient was rendered free of symptoms by the severance of adhesions and the repair of a defect in the skull with a tantalum plate. One patient had considerable improvement in her headache after the drainage of a subdural effusion, by Dr. Elvidge, although she still had symptoms, which were considered to have a neurotic basis. Two patients were relieved of pain by section of the fifth nerve, but in 1 of these, who had a cranial insufflation, an epithelioma of the face developed in the area of denervation, and he never re-turned to work, although he is still living and free from pain. The other patient continued to have dizziness, and even some headaches.

It appears that if a persisting anatomic abnormality is the factor which is holding up the patient's recovery, it should be dealt with, but that one must consider the patient as a whole and his setting before one can be sure that such is the case.

9. VASCULAR RESPONSES TO POSTURE

The responses of pulse and blood pressure to changes in posture have not been included in table 1, as these showed no apparent association with the type or to the presence or absence of headache, although there appeared to be some relation to dizziness. At first, we tried a tilting table test, as described by Weiss,[16] in which the subject was gradually elevated over a period of twenty minutes from a horizontal position to one of 80 degrees from the horizontal. In a study of 26 patients, however, we found that the changes in pulse rate and blood pressure were substantially the same with a simple measurement of these factors after the subject had been lying down for five minutes and then had stood for two minutes. On the basis of previous studies on university students in average physical condition, we concluded that a fall in blood pressure of more than 10 mm. and an increase in pulse rate of more than 20 beats a minute are unusual. Of 89 patients in our series, 28 showed such deviations. Of these 28 patients, 20 had dizziness, but 23 others complained of dizziness without these changes.

These vascular changes appeared to be related to the previous activity of the patient, whether he was in bed or was carrying on at his work, rather than to the severity or the type of the injury, apart from the confinement to bed induced by the injury. A few patients presented normal changes in pulse rate on admission to the hospital, and the deviation increased after they had been in bed for five days, after a pneumoencephalographic test. An increase was observed in a few neurotic patients without head injury and in an occasional healthy person of asthenic build. Such postural changes in pulse have been reported as present in cases of the effort syndrome,[17] and there may be a question whether the alteration is related to sedentary activity or to certain emotional features often present. At any rate, it does not seem related

16. Weiss, S.: Syncope and Related Syndromes, in Christian, H. A.: Oxford Medicine, New York, Oxford University Press, 1943, vol. 2, chap. 8 A, p. 250.

17. Lewis, T.: The Soldier's Heart and the Effort Syndrome, ed. 2, London, Shaw & Sons, Ltd., 1940.

cephalogram was made, and with the results for a few patients on whom direct operative procedures were carried out. The data show the results of 104 procedures carried out on 82 patients, several patients having been submitted to more than one procedure. Of these 82 patients, 34 had returned because of failure of the operation to relieve their symptoms or because of a later relapse. Another 46 patients to whom we sent follow-up letters, and who were subjected to one of the three indirect procedures, including control encephalographic studies, did not reply. The results for these patients might have increased the percentage of cures, lowered as it was by the patients selected because of failure.

The fact remains, however, that we are able to report few cases in which the patient was cured or considerably improved several months to a few years after the procedure. The patients with spinal insufflation, like those with the ordinary pneumoencephalographic study, most frequently showed no essential change which could be attributed to the procedure, while a few who were subjected to this procedure shared with the patients with cranial insufflation a tendency to improvement, with later relapse. This relapse, with both procedures, usually occurred three to eleven months after the operation, the free interval accounting for the previous reports of short term cures. When relief of headache, both permanent and temporary, is considered for the patients with spinal insufflation, the figure (17 out of 40 patients, or 42.5 per cent) corresponds more closely with the results reported by Penfield and Norcross [15] (56 per cent) than does the long term result.

Of the patients subjected to spinal insufflation, shown in table 7, one who was cured of the headache was the corporal in the Royal Canadian Air Force the other factors in whose case have already been discussed; another patient returned because of the persistence of dizziness, but claimed that he had had no headache for two weeks *prior* to the insufflation.

At the suggestion of Prof. Wilder Penfield, and with the help of Prof. Allen O. Whipple, of the department of surgery of the Presbyterian Hospital in New York, we obtained reports on 3 of the 7 patients on whom the method of spinal insufflation was first tried by Penfield.[18] One (case 4 in Penfield's series) had been completely free from symptoms since the insufflation, which was done two months after a minor injury with no unconsciousness, a condition which in

our experience suggests a tendency to spontaneous improvement if personality instability and situational factors are not severe. One patient (case 7) had had frontal headache only a few times a year, and the other (case 2), who had had a return of dizziness, as reported by Penfield, later had both headaches and dizziness until about five years ago, when they gradually cleared up spontaneously, leaving him with diminished vision and weakness of the left side, due no doubt to the cerebral damage from the original injury.

Of our patients cured of headache by cranial insufflation, one had been followed only three months and another only four and one-half months, when he died of pulmonary tuberculosis. In the case of a third patient the previous personality background and dramatic recovery of the sense of smell following the operation suggested that the result may have been psychologic. We have no further information on the fourth patient except that he still had lapses of memory, although his headache was cured.

In the original account of this procedure by Penfield and Norcross,[15] 6 patients were reported on, at a few months to a year and a half after the operation, as follows: patient 1 was better, but not cured; patient 2 was greatly improved, but not cured; patient 3 was improved; patient 4 although cured of headaches still had occasional dizziness; patient 5 had been relieved of the typical headache, and the dizziness was improved but still present, and patient 6, according to a recent report from the family physician, was free from all complaints. A subsequent review of these patients' charts provided the following more recent information: patient 1, after eight months, was still improved; patient 2, after four years, was still improved but had headaches about once a week although these were decreasing in frequency and were brought on chiefly by wet weather or by drinking beer; patient 3, after three years, remained a problem because of mental disturbance and still claimed to have severe headaches; patient 4 wrote to Dr. Penfield three years after operation saying that the headache had returned; patient 5 had a different kind of headache, and a year and a half after the operation the condition was diagnosed as psychoneurosis, and patient 6 returned not long after the receipt of the letter from his physician, claiming that he had had only temporary relief.

Even when we included the patients who presented other factors that might have been responsible for the cure and the patients with only short follow-up observations, the proportion of patients whose headache was cured or

15. Penfield, W., and Norcross, N. C.: Subdural Traction and Post-traumatic Headache, Arch. Neurol. & Psychiat. **36**:75-94 (July) 1936.

tual impairment with severe injuries, and at least a temporary disturbance after less severe injuries, as well as emotional instability, as suggested by our studies with the Rorschach method. These features are linked with the psychic effects of the trauma, the previous personality of the patient and the situational factors to produce an emotional disturbance which may result in any of the symptoms of headache, dizziness, fatigability, irritability, lack of concentration and other mental disturbances so common in psychoneurotic patients. Anxiety or hysterical features may be present with these symptoms, according to the personality of the patient and other circumstances. These symptoms are probably produced through physiologic mechanisms, such as muscular tension and vascular instability, which are not yet fully understood. The emotional disturbance may also modify and prolong the reaction to a more direct mechanism, such as meningeal contusion or adhesions. The headaches related to emotional disturbances tend to be less localized than those associated with the more direct mechanisms. The hysterical forms tend to be bizarre or generalized, and the anxiety forms, bilateral or occipital, although an occasional psychogenic headache may remain localized at the site of injury in cases in which there was no loss of consciousness and the victim remembers where he was hit.

This concept of the mechanisms of headache indicates the importance of treating the patient as a whole, both for the prevention and for the management of post-traumatic symptoms. Neurosurgical precautions in the treatment of the acute injury are beyond the scope of our paper, but psychologic factors during convalescence may be mentioned. A reassuring attitude on the part of the neurosurgeon is desirable in order to allay the fears with regard to intellectual impairment and a possible threat to economic security, but it should not be an unwarranted optimism. If the patient is suffering a temporary impairment of mental efficiency and of emotional control, it is far better to recognize this and to give him an opportunity of getting back gradually to his previous functional level, rather than to lead him to think prematurely that he has made all the recovery he is going to make. Nor is there usually any need to expect a permanent disability, for in many patients the vis medicatrix naturae seems to persist, not only for months but for years after the injury, provided that the background is good and the environmental circumstances are not too adverse.

The treatment of the majority of patients with symptoms persisting for some time after the injury, for whom nothing can be done surgically, is essentially the management of psychosomatic conditions, with special consideration of any problems created by damage to the brain. Careful examination of the patient, careful consideration of the environmental factors and prolonged psychotherapy, all have a place. Palliative and sedative drug therapy will assist in the handling of the anxiety. Participation in relaxing recreation is also helpful. Above all, an "occupational therapy merging into therapeutic occupation," as Dr. Aubrey Lewis [14a] so aptly described it, should be employed. Pension and compensation boards would contribute to ultimate financial saving if they were to invest funds in establishments for the rehabilitation and reeducation of the injured, instead of continuing to pay out permanent partial disability pensions. The end result would be profitable, not only to the boards but to the victims of such injury, who would regain independent individuality instead of remaining precarious parasites on society.

SUMMARY

In a comparison of 68 patients with persisting complaints after head injury and 22 subjects observed after injury who had not presented themselves because of complaints, attention was given to the type of headache, the presence of items in the previous personality background suggesting instability, the severity of injury, the reports of electroencephalographic and pneumoencephalographic abnormalities, certain ratings of "instability" and "disability" as determined by the Rorschach method and situational factors which seemed relevant to the presentation of complaints.

The greatest difference between the patients and the controls lay in the presence of situational factors which might have produced or aggravated psychoneurotic symptoms. This was true for every type of headache. It was also evident that patients with localized headache showed less evidence of previous neurotic background and more evidence of cerebral damage from the injury. This evidence included electroencephalographic records and Rorschach "disability" ratings, with the ratings for severity of injury and pneumoencephalographic changes tending in the same direction, although less significantly. Except for a few patients with hemicranial headache, somewhat resembling migraine, patients with all other types of headache, especially those of bizarre and generalized distribution, showed previous personality instability similar to that of psycho-

specifically to head injury, and certainly not to the headache after such injury, although it is possibly related to the dizziness in some patients.

Malone [18] ascribed the effect of neostigmine to an assumed vascular instability. We conducted a trial of neostigmine [19] with 6 patients who had dizziness and gave a positive response to the postural change. We could see no improvement as compared with the effect obtained with placebo pills given these patients at another time. It appears that the confidence of the physician in such a measure must be ruled out before the pharmacologic action can be given the credit. It is of interest that with large doses of neostigmine (3 cc. of a solution containing 0.0005 Gm. of neostigmine methylsulfate per cubic centimeter, covered with $\frac{1}{100}$ grain [0.6 mg.] of atropine sulfate, injected subcutaneously) in 2 of these patients we reduced the postural

tients have been helped by these exercises, perhaps in part psychologically, but we have seen the treatment fail with some patients because they still had unsolved personal difficulties. We have seen other patients helped as much by engaging in exercises for relaxation of large muscles, such as walking, dancing, gymnastics and swimming.

10. MECHANISMS, WITH IMPLICATIONS FOR MANAGEMENT

The factors which appear to be related to the production of symptoms in the patients we have studied are shown graphically in the diagram. Every injury to the head involves trauma, both physical and psychic. The physical effects are exerted on the meninges and the brain. Meningeal contusion and meningeal adhesions may be directly responsible for a localized type of head-
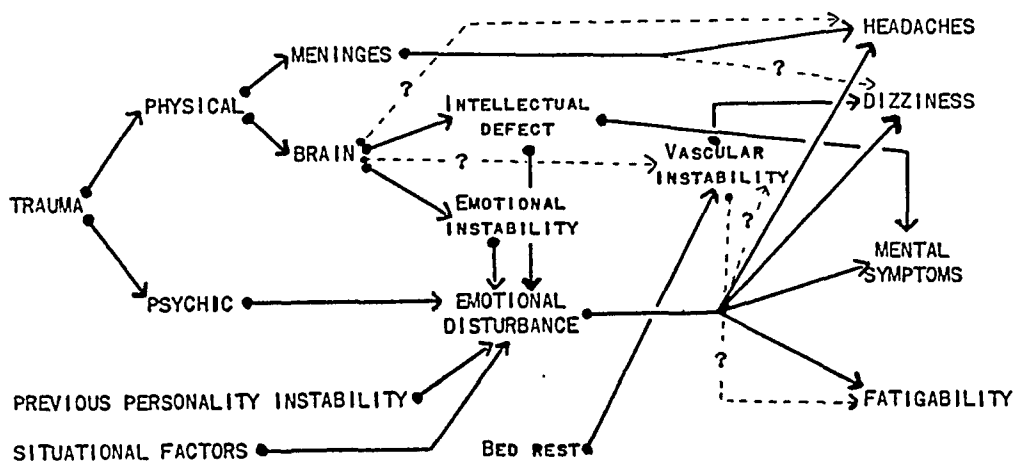
Diagram showing relation of various factors to the production of symptoms in patients with post-traumatic headache.

change in pulse rate—in 1 patient from 76 to 48 beats a minute and in the other from 38 to 32, but without alteration in their headache. In the second patient the pulse rate fell 14 beats after he returned to work. By the use of sodium nitrite we were able to increase the postural change in the pulse rate and the drop in blood pressure so that we could produce fainting in some patients, but we did not consider that this phenomenon was specific for post-traumatic conditions.

A routine of "tension exercises" has been prescribed for some time at this clinic by Dr. Cone, on the basis of the value of improved muscular tone in reducing a tendency to vascular instability. Undoubtedly, many pa-

ache mediated largely through the nerve supply to the dura from the fifth nerve.[20] This headache may clear up spontaneously if no other factors are in operation. It may persist for anatomic reasons and require surgical intervention, but the persistence may have an emotional basis, which is discussed later. Meningeal adhesions might also be responsible for dizziness, although such a cause is not well established. Localized headache may be produced by cerebral contusion, although we do not know what the anatomic pathways would be in such a case. Many of the localized headaches appeared to wax and wane with the presence and absence of fatigue and emotional stress, a feature suggesting a relation to cerebral function rather than to meningeal adhesions, although changes in intracranial circulation might provide the connecting link. Other effects on the brain include intellec-

18. Malone, J. Y.: Head Injuries: New Treatment for Postconcussional Headaches and Dizziness; Preliminary Report, J. A. M. A. **119**:861-864 (July 11) 1942.

19. The neostigmine used in this study was donated by Hoffmann-LaRoche, Ltd., Montreal.

20. Penfield, W., and McNaughton, F. L.: Dural Headache and Innervation of the Dura Mater. Arch. Neurol. & Psychiat. **44**:43-75 (July) 1940.

THE ELECTROENCEPHALOGRAM ASSOCIATED WITH EPILEPSY

CAPTAIN FRANCIS A. ECHLIN

MEDICAL CORPS, ARMY OF THE UNITED STATES

The present paper deals chiefly with the interpretation of the electroencephalogram when used as a diagnostic aid in the study of epileptic patients between seizures.

Hughlings Jackson [1] remarked:

I submit that it is well also to consider that the warning in any paroxysm signifies the seat of a discharging lesion, that the warning is in that sense localizing.

Electroencephalography has shown that even preceding the warning there is frequently a localized abnormal electrical discharge from the brain, and in many cases this occurs almost constantly as a subclinical phenomenon. One therefore has an opportunity in a large number of instances of discovering the "seat" of origin of the potential changes, especially if the patient is studied between clinical seizures, when this may be localized, rather than at the height of a convulsion, when the electrical disturbance, like the clinical manifestations, may be generalized.

The problem of the electroencephalographic classification of the epilepsies has been approached from two standpoints. Gibbs, Davis and Lennox,[2] who pioneered in this field, showed that certain wave forms and patterns are frequently present during certain varieties of clinical seizures, and Gibbs, Gibbs and Lennox [3] proposed a classification based on these and other criteria. For instance, they stated:

A fast rhythm spells grand mal, a slow rhythm psychomotor and an alternating slow and fast rhythm petit mal epilepsy.[3b]

Jasper and Kershman,[1] in attempting to use this classification in routine examinations of epileptic patients between seizures, reported that they could not accurately predict the form of the clinical attack from the wave forms and patterns seen in the electroencephalogram. They therefore undertook the problem anew. They carried out extensive localization studies on each patient, and as a result they concluded that localization of the abnormal discharge provided the most satisfactory basis for classification of the electroencephalographic records, with wave forms and patterns playing a secondary role in the detailed analysis of each case.

Evidence for and against the usefulness of these two classifications is found in the literature and will be outlined here. Walter,[5] by using the phase reversal technic introduced by Adrian and Yamagiwa,[6] was the first to demonstrate that an organic lesion of the brain, such as a tumor, reveals itself in the electroencephalogram by the presence of localized delta waves. Since then evidence has accumulated which shows that an epileptic cortical focus may likewise be localized (Golla, Graham and Walter [7]; Jasper and Hawke [8]; Gibbs, Gibbs and Lennox [3b]; Case [9]; Case and Bucy [10]; Jasper and Kershman [4]; Penfield and Erickson [11]; Gibbs; Merritt and Gibbs,[12]

1. Jackson, J.: On Epilepsy and Epileptiform Convulsions, in Taylor, J.; Holmes, G., and Walshe, F. M. R.: Selected Writings of John Hughlings Jackson, London, Hodder & Stoughton, Ltd., 1931, vol. 1.

2. Gibbs, F. A.; Davis, H., and Lennox, W. G.: The Electroencephalogram in Epilepsy and in Conditions of Impaired Consciousness, Arch. Neurol. & Psychiat. 34:1133-1148 (Aug.) 1935.

3. (a) Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: A Cerebral Dysrhythmia, Brain 60:377-388, 1937; (b) Cerebral Dysrhythmias of Epilepsy, Arch. Neurol. & Psychiat. 39:298-314 (Feb.) 1938.

4. Jasper, H. H., and Kershman, J.: Electroencephalographic Classification of the Epilepsies, Arch. Neurol. & Psychiat. 45:903-943 (June) 1941.

5. Walter, W. G.: The Location of Cerebral Tumors by Electroencephalography, Lancet 2:305-312, 1936.

6. Adrian, E. D., and Yamagiwa, K.: Origin of Berger Rhythm, Brain 58:323-351, 1935.

7. Golla, F.; Graham, S., and Walter, W. G.: The Electroencephalogram in Epilepsy, J. Ment. Sc. 83:137-155, 1937.

8. Jasper, H. H., and Hawke, W. A.: Electroencephalography in Localization of Seizure Waves in Epilepsy, Arch. Neurol. & Psychiat. 39:885-890 (May) 1938.

9. Case, T. J.: Electroencephalography in the Diagnosis and Localization of Intracranial Conditions, J. Nerv. & Ment. Dis. 87:598-602, 1938.

10. Case, T. J., and Bucy, P. C.: Localization of Cerebral Lesions by Electroencephalography, J. Neurophysiol. 1:245-261, 1938.

11. Penfield, W., and Erickson, T. C.: Epilepsy and Cerebral Localization, Springfield, Ill., Charles C Thomas, Publisher, 1941.

neurotic patients and evidence of "instability" in the Rorschach test resembling that found for neurotic patients. The evidence for patients complaining of symptoms other than headache also tended to resemble that for neurotic patients.

A follow-up study of 82 patients with post-traumatic symptoms previously treated in this institute indicated that the long term results with spinal or with cranial subdural insufflation have been no better than the results following pneumo-encephalographic treatment, and that for none of these patients could the influence of other factors be ruled out. The results in a few patients treated by a direct operative procedure suggest a limited application of such measures in carefully selected cases.

Studies of the postural vascular responses did not indicate any effect in patients with head injury which differed from that in psychoneurotic patients or in patients convalescing from other illness, nor have they given any lead to treatment other than to suggest the value of exercises for hardening and relaxation.

The concept of mechanisms presented here involves a relation between physical and psychologic factors and emphasizes the need of considering the person as a whole in the prevention and cure of post-traumatic symptoms.

3801 University Street.

localized cortical electrical abnormalities was so high (30 per cent).

A four channel, ink-writing electroencephalographic apparatus, built by Rahm, was used throughout. The apparatus was in one room and the patient in an adjoining one, which contained the input for the electrodes. This was connected to the amplifiers by means of a cable. Both rooms were electrically shielded, having been completely lead lined previously for use as x-ray rooms. They were shielded from one another by a grounded copper screen door. Nine electrodes were routinely used on each side of the head (fig. 1), and the placements were the same as those described by Jasper, Kershman and Elvidge.[18] Special electrodes were applied when indicated for localization. Localization studies were carried out on all patients, with the phase reversal technic, and bilateral recording was used during a considerable portion of the examination. Records were taken for one hour or more from most of the patients, the greater part of a morning or an afternoon being devoted to the study of each patient. The patient hyperventilated for four or five minutes during the study, and tracings were taken at intervals during this period.
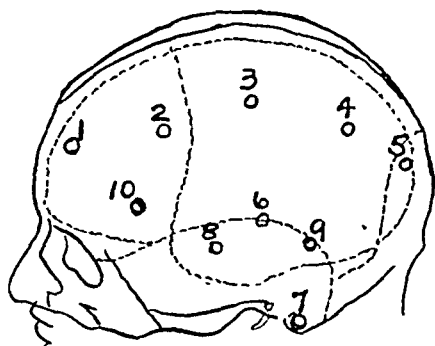
Fig. 1.—This diagram illustrates the position of the electrodes used in the present study. Placements *1* to *9* were employed (on both sides of the head) routinely in each case. The position of the electrodes is indicated (by numbers) to the left of the tracings in the following figures, and should be compared with figure 1 for proper interpretation.

Measurements used in the placement of electrodes were the same as those described by Jasper, Kershman and Elvidge.[18]

A sphenoid lead of the type used by Grinker and Serota [19] and by Jasper (cited by Penfield and Erickson [11]) to advantage in demonstrating the deep central origin of bilaterally synchronous potentials, was not employed in this study.

Miss Alice Wiltsek and Miss Share gave technical help in obtaining the records.

RESULTS

The most outstanding feature of the abnormal discharges recorded from epileptic patients was the recurring or paroxysmal appearance of high voltage waves, a phenomenon termed paroxysmal

hypersynchrony by Jasper and Nichols.[20] Most, but by no means all, of these potential changes occurred at frequencies which may be regarded as abnormal, and therefore, in addition there was frequently dysrhythmia, as stressed by Gibbs, Gibbs and Lennox.[3]

It can be stated here that, although the discharges just mentioned constituted the outstanding feature of the records studied, similar abnormal waves (with the possible exception of the 3 per second wave and spike pattern) were seen in patients who did not have clinical epilepsy and it was therefore usually felt unwise to make a diagnosis of epilepsy from the electroencephalogram alone.

I. CLASSIFICATION OF ELECTROENCEPHALOGRAMS ACCORDING TO LOCALIZATION OF THE DISCHARGE

Under this heading are reported the results of an attempt to classify the electroencephalograms of 100 patients with a history of convulsions according to the Jasper-Kershman [4] classification. These authors reported that from the standpoint of localization three principal kinds of abnormal activity are observed in epileptic patients, namely: (1) localized (unilateral cortical), (2) bilaterally synchronous (from homologous areas of the right and the left hemisphere) and (3) diffuse.

In the present study it was found that the records taken from the 100 patients could be divided with a considerable degree of accuracy into the three chief types just mentioned. In addition, 20 per cent of the patients had what was regarded as a normal electroencephalogram.

Localized Unilateral Cortical Abnormality (30 per cent of patients)—In 30 of the patients studied between clinical seizures an abnormal discharge was recorded from a relatively restricted area over one cerebral hemisphere. The unilateral nature of the abnormalities in these epileptic patients immediately differentiated them from the bilateral changes in the electroencephalogram, to be described later. On figure 2 samples of subclinical unilateral discharges from 8 patients are shown.

It may be restated here that the patients examined were a selected group. When patients were referred from other hospitals, usually only those with a history or signs suggestive of focal epilepsy (12 patients) were chosen, and hence 30 per cent is not a true estimate of the number in an unselected group of epileptic patients who would have shown a localized abnormality in the

18. Jasper, H. H.; Kershman, J., and Elvidge, A.: Electroencephalographic Studies of Injury to the Head, Arch. Neurol. & Psychiat. **44**:328-350 (Aug.) 1940.

19. Grinker, R. R., and Serota, H. M.: Studies on Corticohypothalamic Relations in the Cat and Man, J. Neurophysiol. **1**:573-589, 1938.

20. Jasper, H. H., and Nichols, E. C.: Electrical Signs of Cortical Function in Epilepsy and Allied Disorders, Am. J. Psychiat. **94**:835-850, 1938.

and others). The article by Casamajor and associates [13] should, perhaps, be added to this group, but these authors found that in a series of cases of unilateral seizures in children the abnormal rhythms, although tending to be more prominent in the hemisphere opposite the side of the convulsions, were always diffuse.

Concerning the interpretation of other aspects of the electroencephalogram in cases of epilepsy agreement is not so close. First, there is the difference of opinion expressed by Jasper and Kershman [4] and Gibbs and associates [3b] with respect to the value of wave patterns as diagnostic criteria, as previously mentioned. Rheinberger [14] favored the Jasper-Kershman point of view, and Hoefer [15] found much of value in the Gibbs-Lennox classification. In addition, Finley and Dynes,[16] in a recent review of the electroencephalograms of 369 patients with convulsive seizures, stated:

Because of the great variety of patterns obtained in epileptics, and because many of these patterns resembled those found in other disorders, the use of clinical terminology in describing the brain wave patterns of epileptics is misleading.

These authors did not find the Jasper-Kershman or the Gibbs-Lennox classification satisfactory and stated the opinion that "the time has not yet arrived to make any formal classification of brain wave patterns." Finley,[17] in an analysis of 4,500 cases of neuropsychiatric disorders, also reported that he found rapid frequency cycles of the type described by Gibbs and associates as associated with grand mal to be more common with the involutional and manic-depressive psychoses and with neurosyphilis than with epilepsy.

The work to be reported is an attempt to interpret the electroencephalograms of 100 epileptic patients in the light of the conflicting observations and opinions just outlined. The first part of the study was devoted to an effort to classify the electroencephalographic records according to the localization of the abnormal discharges in the brain, as outlined by Jasper and Kershman,[4] and to tabulation of various wave forms and patterns seen, as described by Gibbs, Davis and Lennox [2] and Gibbs, Gibbs and Lennox.[3b] The results were correlated with the available clinical data, and certain conclusions were drawn.

With this information accessible concerning the localization of the abnormal waves and the types of clinical seizures of the individual patients, an endeavor was made to determine the significance of the slow wave patterns, so often seen, and described by Gibbs, Gibbs and Lennox,[3b] as of the "psychomotor" type. In addition, the possible significance of the so-called grand mal and petit mal wave patterns and of the frequency of the various waves is considered on the basis of these data. Finally, the nature of the neuron discharges which summate to form the high voltage waves in epilepsy is discussed.

It will be seen that the first part of the paper represents a repetition of the work of Jasper and Kershman.[4] This was necessary before the study reported in the second part of the article could be undertaken.

MATERIAL AND TECHNIC

One hundred and ninety electroencephalograms obtained during the past two and one-half years from 100 patients with a history of convulsive seizures were studied. The patients were all examined between seizures, but a number of them had clinical attacks during the recording. When this happened, a second examination was made later, so that tracings were obtained when the patient had been free of seizures (other than petit mal) for twenty-four hours before or after the taking of a record.

The neurologic and neurosurgical outpatient clinic at Lenox Hill Hospital, New York, provided the greatest source of the material. Patients in this group who showed focal cortical abnormalities were admitted to the neurologic-neurosurgical service for encephalographic study and more complete neurologic and electroencephalographic examination. In addition, a clinic was held at Lincoln Hospital for six months, and all patients with a clinical history of seizures suggesting a focal cortical onset were brought for electroencephalographic study through the outpatient department at Lenox Hill Hospital. A number of these patients were also admitted to the neurologic service for further investigation. A few patients with convulsive disorders were referred from Bellevue Hospital, and a group of patients were studied through permission of private physicians. A number of the last group were also referred for study because of a history of focal epilepsy.

The selection of patients with a history, and frequently neurologic signs, suggestive of a focal onset of their convulsions explains why the number showing

12. Gibbs, E. L.; Merritt, H. H., and Gibbs, F. A.: Electroencephalographic Foci Associated with Epilepsy, Arch. Neurol. & Psychiat. **49**:793-801 (June) 1943.

13. Casamajor, L.; Smith, J. R.; Constable, K., and Walter, C. W. P.: Electroencephalogram of Children with Focal Convulsive Seizures, Arch. Neurol. & Psychiat. **45**:834-847 (May) 1941.

14. Rheinberger, M., in discussion on Echlin, F. A.: The Electroencephalogram in Epilepsy, Arch. Neurol. & Psychiat. **49**:296-299 (Feb.) 1943.

15. Hoefer, P. F. A., in discussion on Echlin, F. A.: The Electroencephalogram in Epilepsy, Arch. Neurol. & Psychiat. **49**:296-299 (Feb.) 1943.

16. Finley, K. H., and Dynes, J. B.: Electroencephalographic Studies in Epilepsy, Brain **65**:256-265, 1942.

17. Finley, K. H.: Potentials of Rapid Frequency in the Human Electroencephalogram, Arch. Neurol. & Psychiat. **49**:308-310 (Feb.) 1943.

electroencephalogram. Eight of the 30 patients were known to have a relatively localized organic lesion of the brain before electroencephalographic studies were undertaken. (These lesions were healed cerebral abscess, 2 patients; traumatic meningocerebral cicatrix, 3 patients; cerebral cicatrix, 2 patients, and tumor of the brain, 1 patient).

Jasper and Kershman[4] described four paroxysmal wave forms as being most typical of a localized cortical discharge, namely, random spikes (L 1), random sharp waves (L 2). delta waves (L 3) and occasional local paroxysmal rhythms (L 4) of 10 or more per second type.

In this study, random high voltage spikes were recorded from only 2 patients and these were of longer duration (about fifty milliseconds) than the spikes described by Jasper and Kershman.[4] Sharp waves were the outstanding feature in the tracings of 24 patients (26 if the 2 subjects showing spikes are included) and delta waves, in the records of 4 patients; but the latter also occurred with most of the other localized disturbances. Unilateral paroxysmal rhythms (at 3 to 6 per second) were prominent in the records of 5 of these patients, but briefer discharges of rhythmic slow waves were noted in the records of a much larger group (more than 50 per cent of patients) and will be discussed in detail later. Examples of each of these wave forms are shown in figure 2. Rhythmic waves at 14 per second or higher were seen in the records of 3 patients.

In all 30 patients the aforementioned abnormalities were observed as a subclinical phenomenon (without having the patient hyperventilate) in the absence of seizures for twenty-four hours before or after the tracing was taken. In fact, these localized discharges occurred as an almost constant phenomenon in over 65 per cent of the (30) patients with the unilaterally abnormal electroencephalogram. The subjects who had seizures during the taking of a record were studied again later. Hyperventilation, as described in the section on "Material and Technic," was used with all patients, and in over 50 per cent it caused some increase in the localized activity, either during or shortly after it was completed.

It was previously stated that the abnormal discharge was recorded from a relatively restricted area. This area, with no exception, was at least 4 cm. in diameter and varied of course with the intensity of the activity. When this increased, which occurred at some time in over 75 per cent of subjects, some effect was noted on the waves in the opposite hemisphere. By means of the phase reversal technic, the approximate point at which the potential gradients came to a focus could be determined with considerable accuracy to within an area about 4 cm. in diameter. It is true that in many cases the margins of this focus appeared to shift at certain intervals from 1 to 3 cm. during a single recording, as observed by Hoefer[15] and others. Shifts greater than this were not noted in subsequent electroencephalograms from the same patient.

Bilaterally Synchronous Abnormality (35 per cent of patients).—In 35 of the epileptic patients studied between seizures intermittent or paroxysmal bursts of high voltage waves appeared simultaneously from homologous areas in the two hemispheres, as described by Jasper and Kershman. In the records of about 40 per cent of patients hyperventilation was necessary before these abnormalities became evident. The bilaterality (location) of the disturbance clearly distinguished these patients from those who showed unilateral abnormality. The findings are in agreement with Jasper and Kershman's[4] hypothesis that "a common central (midline subcortical) pacemaker is a necessary hypothesis to account for this synchronization of bilateral discharge when there is no evidence for one hemisphere leading the other."

Jasper and Kershman[4] stated:

Paroxysmal rhythms are the most common forms of bilaterally synchronous activity. The most perfect bilateral synchrony is seen in the 3 per second wave and spike pattern (B3 and 1), 3 per second waves (B3) and 6 per second waves (B 4). The only random waves that show a fair bilateral synchrony are the sharp waves (B 2) from the temporal lobes, but even here they tend to become rhythmic (frequencies between 3 and 6 per second) when showing bilateral synchrony.

These observations held true in the present study. An analysis of the records, based on their classification, follows. Examples of the four important paroxysmal rhythms seen in the records of patients with bilaterally synchronous abnormality are shown in figure 3.

Three per Second Wave and Spike (B 3 and 1) Activity: Seven records showing 3 per second wave and spike pattern were obtained from different patients between clinical seizures (figs. 3 and 4).

Sharp Waves (B 2) Activity: Bilateral sharp waves from the region of the temporal lobes were obtained from 14 patients between clinical attacks.

Three per Second (B 3) Activity: Abnormality of this type was present as the outstanding feature in the records of 13 patients (fig. 3). In 2 patients the 3 per second wave activity was
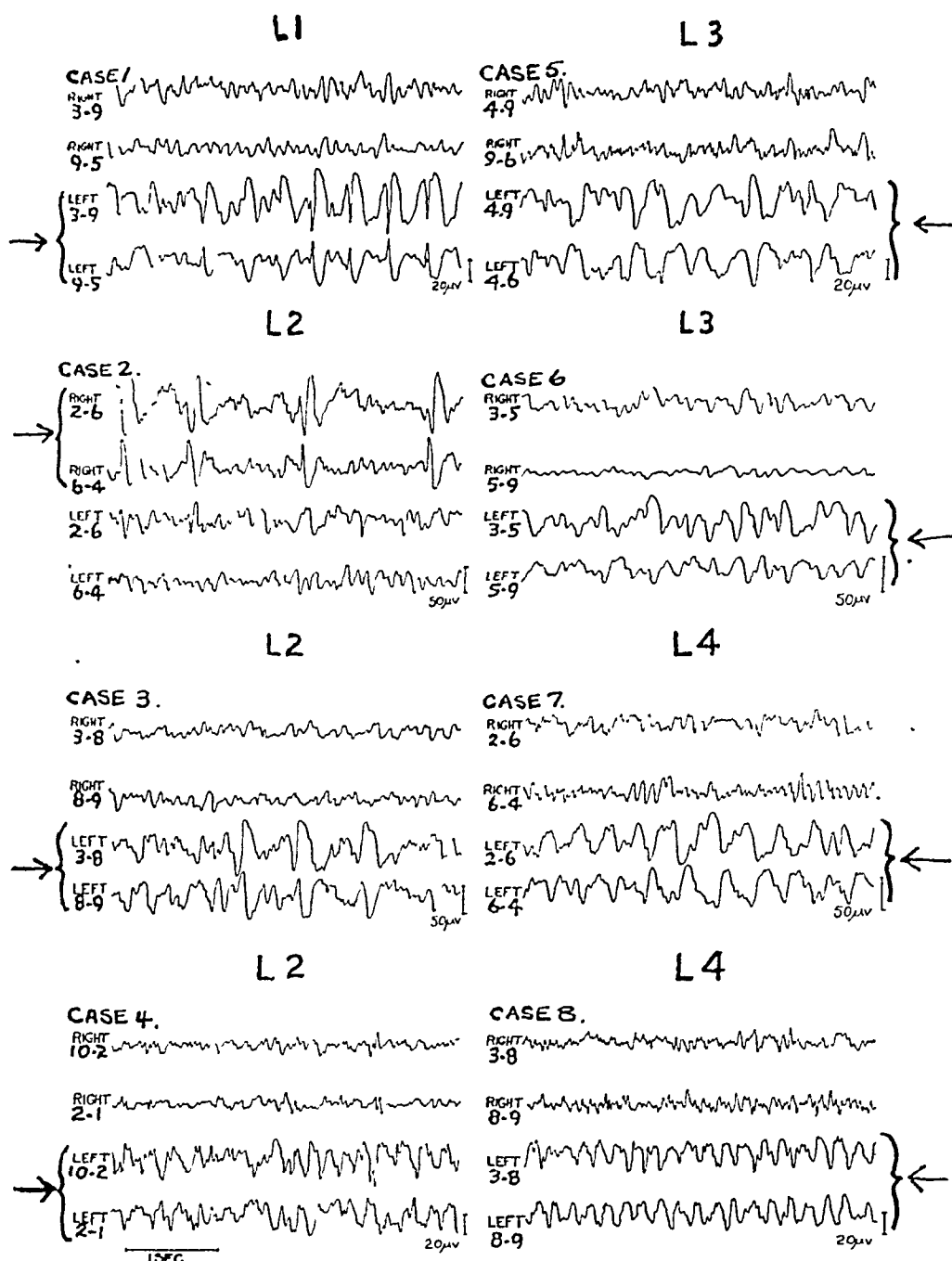
Fig. 2.—Samples of subclinical unilateral "focal" cortical abnormal discharges from 8 epileptic patients. For all patients tracings of the electrical activity were taken simultaneously from the two sides of the head, the upper two lines in each case representing the activity from the right side, and the lower two lines, that from homologous areas on the left side. The abnormal discharge is indicated by an arrow in the individual cases; this is confined to one side of the head, the left except in case 2.

The three common types of abnormal waves are illustrated in the tracings: *L 1*, spikes; *L 2*, sharp waves, and *L 3*, delta waves.

The distinguishing feature of the "focal" cortical abnormalities is their unilateral localized nature, and not the wave forms or patterns present, since these vary in form and frequency from moment to moment.

In cases 7 and 8 samples of rhythmic discharges (*L 4*) similar to those described as "psychomotor" by Gibbs, Gibbs and Lennox[3] were taken. In 3 of the other cases (1, 4 and 6) rhythmic slow waves patterns at 3 to 6 per second are also present, indicating the tendency of most discharges (in 50 per cent of cases with high voltage potentials in this study) at some time to take on a slow rhythmic form. Similar 3 to 6 per second waves are shown in 2 cases in figures 6 and 7.

Note the similarity between the unilateral 3 per second waves in case 7 and those in figure 3, case 5, and in figure 4, *3*, in which the waves are bilaterally synchronous. It will be seen, also, that the unilateral potentials in case 4 resemble the bilateral ones in figure 3, case 3.

The term "psychomotor" has been used in referring to all 3 to 6 per second rhythmic slow waves because of their essential similarity to one another and to the "psychomotor" pattern of Gibbs and associates,[3b] but it is not advocated that this clinical term be so used in the future.

That the potentials in certain instances presented at intervals·a square top did not appear a sufficient criterion to warrant the separation of these patterns from the others into a so-called psychomotor group.

Electrode numbers are noted to the left of each tracing. Placement of electrodes is shown in figure 1.

pronounced increased intracranial pressure fell into the same category.

However, 15 per cent of the patients did show a slight diffuse abnormality in the electroencephalogram (fig. 5). The characteristics of this disturbance were a moderate variation in the voltage and frequency of the alpha rhythm and the presence of scattered random delta waves of low

CORRELATION OF ELECTROENCEPHALOGRAPHIC AND CLINICAL DATA.

Under this heading the clinical data concerning the variety or pattern of the epileptic seizure are correlated with the location of the discharge in the brain and with the wave pattern seen in the records of certain patients. This represents a repetition of Jasper and Kershman's [4] work.
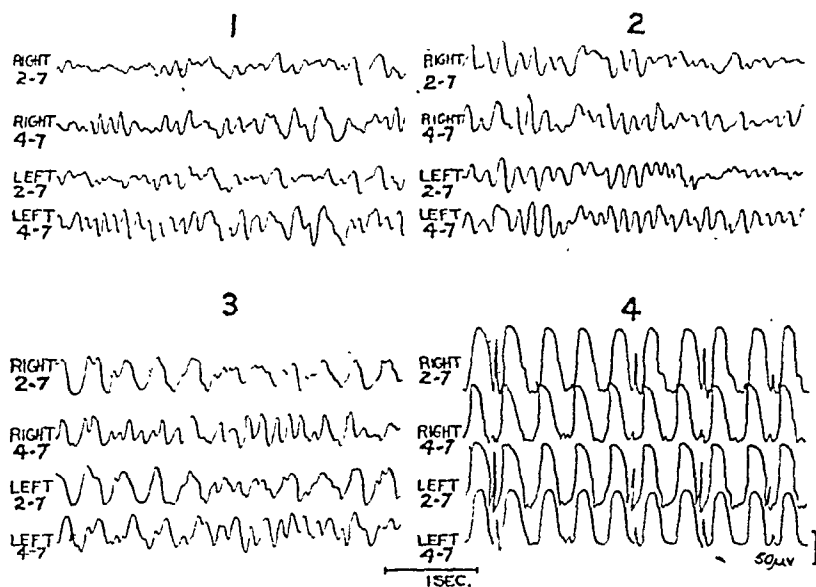
Fig. 4.—These four tracings were recorded at various intervals from the same patient. The activity is of the bilaterally synchronous type. The frequencies fluctuate between 9 and 3 per second (see text for explanation).

The slow (3 per second) waves in tracing 3 appear essentially the same as those described as "psychomotor" by Gibbs, Gibbs and Lennox (fig. 3, tracing 18 [3b]). This is interesting, for, as will be seen, in tracing 4, taken thirty seconds later, the slow potentials are replaced by a subclinical 3 per second wave and spike pattern (so-called petit mal abnormality). This pattern may be compared with the waves in figure 2, case 7.

This patient had clinical attacks of petit mal and grand mal and periods of mental dulness. His electroencephalogram presented, almost constant abnormality, but of fluctuating degree.
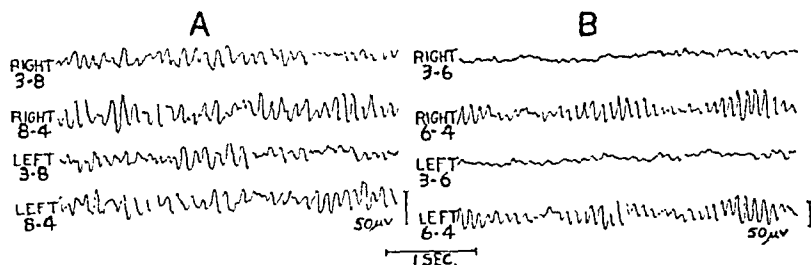
Fig. 5.—Record A shows a slight diffuse abnormality, and B is a normal electroencephalogram (see text for explanation).

voltage. These abnormalities frequently occurred in bilaterally synchronous fashion. Discharges of rapid low amplitude sharp waves at 14 to 25 per second were occasionally present. A dividing line could not always be drawn between records of this type and an electroencephalogram judged to be normal. The 3 patients with more conspicuous diffuse abnormality were included in the 15 per cent.

Normal Electroencephalograms.—Twenty per cent of the epileptic patients studied had normal records (fig. 5).

Classification by Clinical Seizure Pattern.— In classification of the various forms of clinical seizures an endeavor has been made to employ the terms "psychomotor," "psychic variant or equivalent" and "amnesia" in the sense in which Gibbs, Gibbs and Lennox [3b] used them. However, it is probable that many of the attacks placed in this category would not be regarded as "psychomotor" by Gibbs and associates because of their minor nature. In part II of the paper the clinical and electroencephalographic aspects of such episodes will be discussed in more detail.

replaced by a 3 per second wave and spike pattern during a clinical seizure, and their records were therefore classified as having a bilaterally synchronous 3 per second wave and spike pattern.

In patients who showed bilaterally synchronous 3 per second wave or 3 per second wave and spike activity it was usually noted that between bursts of the high voltage waves the normal potentials were disturbed by fluctuations in amplitude and frequency. At times the alpha

hence the record might be mistaken for, and classified as, one showing diffuse nonlocalized activity.

Rhythmic Six per Second (B 4) Activity: Rhythmic waves at 3 to 6 per second will be described later. One patient had only intermittent discharges of 6 per second smooth waves, and this record was therefore not included with any of the foregoing types.

Diffuse Nonlocalized Activity (15 per cent of patients).—Only 3 patients showed diffuse
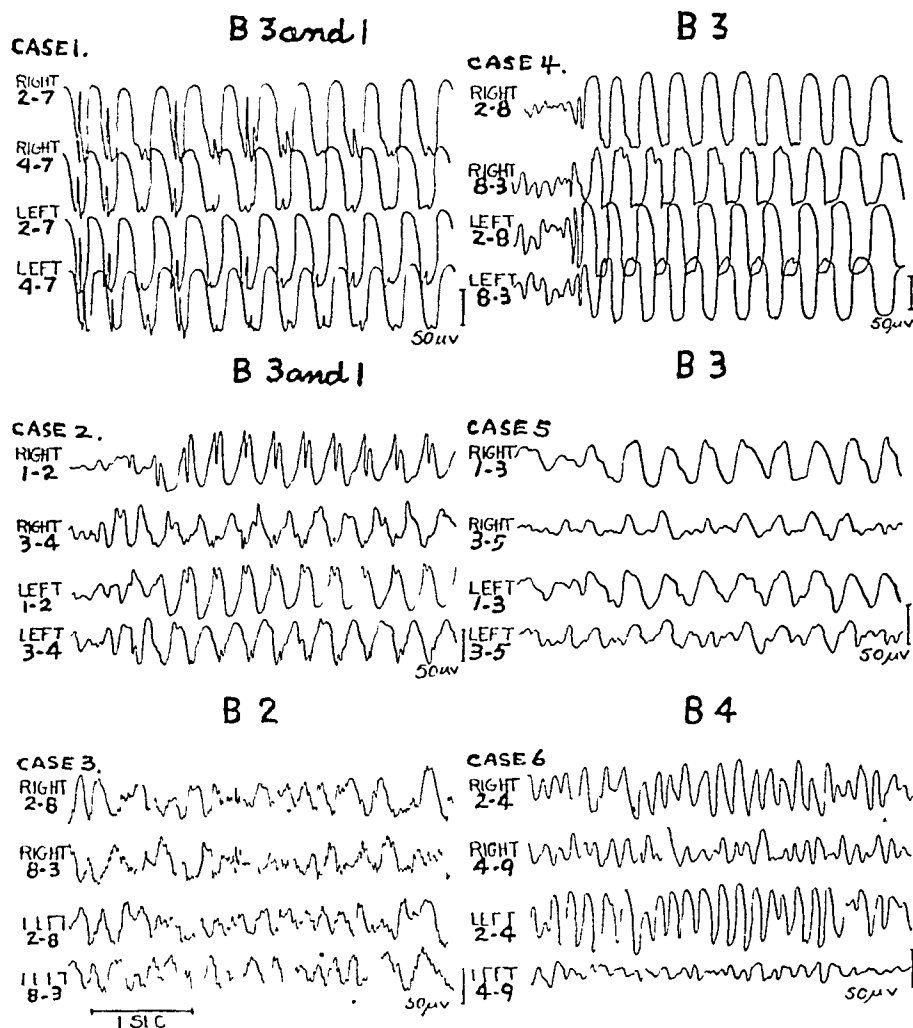
Fig. 3.—Discharges of the bilaterally synchronous type taken from 6 patients. B 3 and 1 is an example of 3 per second wave and spike activity; B 2, of sharp waves; B 3, of 3 per second waves; and B 4, of 6 per second waves. The abnormal potentials in these cases appear simultaneously from the two hemispheres, in contrast to the potentials shown in figure 2, which were confined to one side of the head. In cases 3 and 5 the potentials are similar to those described as "psychomotor" by Gibbs and associates.[3b] Note the similarity between the wave patterns in these cases (3 and 5) and the rhythmic activity shown in figure 2. Tracings were taken simultaneously from the two sides of the head. The upper two lines in each case are from the right side of the head, and the lower two lines, from homologous areas on the left side. Electrode numbers are indicated to the left of each tracing, and their placements are shown in figure 1 (see text).

rhythm was replaced by waves fluctuating between 3 and 9 per second, as shown in figure 4. In some cases the abnormality was slight and was confined to the changes shown in figure 4, 2, even during hyperventilation, and only on subsequent recording were sudden bursts of typical large voltage 3 per second wave and spike activity seen. In view of these observations, it appears that a relatively quiescent, deep, apparently midline focus may produce only a slight effect (diffuse disorganization) on the cortical rhythms, and

nonlocalized abnormal activity similar to that described by Jasper and Kershman.[4] Two other patients showing such changes were excluded from the present series, as they were known to have gross diffuse lesions of the brain, and the presence of delta waves made interpretation of the records uncertain. It should be added that no children under 10 years of age were included in this study because of the difficulty in interpretation. Patients who had just recovered from an epileptic seizure and those in stupor or with

the lesion was at or near the site indicated by the electroencephalogram. Twenty-four (80 per cent) of the 30 patients included in the series gave a history of grand mal attacks; 12 patients had "psychomotor" attacks, "psychic variant or equivalent" states or episodes of "amnesia," and 1 patient, petit mal. The average age of the patients in this group was 25 at the time of study.

Clinical Seizures Associated with Bilaterally Synchronous Activity (35 patients).—Thirty (85.7 per cent) of the patients with electroencephalographic abnormalities of this type had grand mal seizures, and 28 (80 per cent) had such attacks without any clinical pattern to suggest an origin in a focal area of the cortex. Two patients (5.7 per cent) gave a history of attacks the focal clinical pattern of which suggested an origin in the temporal lobe, and these patients had bilaterally synchronous sharp wave (B_2) activity. Twelve (34.2 per cent) of the patients had petit mal, and 15 (42.8 per cent) "psychomotor" attacks, "psychic variant or equivalent" states or episodes of "amnesia."

Bilaterally Synchronous Three per Second Wave and Spike (B 3 and 1) Activity: Seven patients had this electroencephalographic pattern. All of them had grand mal attacks without localizing features, and 5 gave a history of petit mal attacks as well. One patient also had "psychomotor" episodes.

Bilaterally Synchronous Three per Second (B 3) Waves: Thirteen patients showed electroencephalographic patterns of this type. Nine of the patients had generalized grand mal seizures, 5, petit mal seizures and 6, "psychomotor" attacks, "psychic variant or equivalent" states or episodes of "amnesia." Three patients gave a history of petit mal attacks only, without any grand mal seizures. Patients showing the B 3 and 1 or B 3 type of abnormality had an average age at the onset of their attacks of 12 years, and their average age at the time of study was 18 years.

Bilaterally Synchronous Sharp Waves (B 2): Fourteen patients had electroencephalographic patterns of this type. Thirteen patients gave a history of major seizures. Eight patients had "psychomotor" attacks, "psychic variant or equivalent" states or spells of "amnesia," in addition to grand mal seizures, and 2 patients had petit mal, as well as grand mal, seizures. In 2 patients the pattern of the attacks was focal (symptoms suggesting an origin in the temporal lobe).

Rhythmic Three to Six per Second (B 4) Waves: This pattern will be considered later.

Clinical Seizures Associated with Slight Diffuse Abnormality or Normal Electroencephalograms.—Thirty-five patients (35 per cent) had such records. As previously mentioned, it was difficult to draw a dividing line between many of the records showing a slight diffuse abnormality and normal electroencephalograms. This was equally true in clinical analysis. The patients have therefore been analyzed as a group.

Thirty-two (91.4 per cent) of the patients had grand mal epilepsy; 7 patients had "psychomotor" attacks, "psychic variant or equivalent" states or episodes of "amnesia"; 6 had petit mal, and 5 had focal clinical seizures. Twenty-seven patients gave a history of grand mal without any clinical localizing features.

The average age at the onset of attacks in this group was 26, and the average age at the time of study was 37.

Comment.—From the form of the electroencephalogram (classified according to localization of the disturbance) guarded predictions can be made concerning the type of clinical seizure with which it may be expected to be associated.

1. When a localized cortical disturbance was present, one could surmise for a high percentage of patients (70 per cent in this study) that focal clinical seizures would be associated. However, 40 per cent of these same patients had "psychomotor" attacks (psychic equivalent or variant or amnesia states), and 80 per cent had grand mal episodes in addition.

2. When bilaterally synchronous waves were the outstanding feature in the electroencephalogram, grand mal seizures, without localizing features, were the rule (80 per cent of patients), and petit mal attacks were common (34.2 per cent). Of the patients with a history of grand mal, 93.3 per cent (28 of 30 patients) had such seizures, without any clinical evidence to suggest that they originated in a localized area of the cortex. These observations are in keeping with the hypothesis that the origin of the electrical abnormality lies deep in the brain in these cases. "Psychomotor" seizures were also frequent (42.8 per cent) in this group.

3. Patients with normal electroencephalograms or a slight diffuse electrical disturbance (relatively quiescent abnormal activity) had seizures essentially similar to those in the preceding group except that clinical attacks of the focal cortical type were a little more frequent (14.3 per cent).

II. WAVE PATTERNS ASSOCIATED WITH EPILEPSY

Gibbs, Davis and Lennox[2] and Gibbs, Gibbs and Lennox[3b] observed that certain wave patterns were present during particular types of

Clinical seizures were considered to be of the focal cortical or of the petit mal type, according to the criteria outlined by Penfield and Erickson.[11] Petit mal attacks are presumably due to a disturbance originating deep near the midline of the brain and as a rule are apparently represented in the electroencephalogram by bilaterally synchronous abnormal waves when an active discharge is present. Minor attacks commencing in a localized area of the cortex, such as might result from a discharge in the region of the left temporal lobe, may give rise to a transitory sensory aphasia (disorientation, confusion and transitory disturbance of consciousness). Such a minor attack is not usually regarded in this paper as a petit mal seizure but, rather, is considered as a "psychomotor" (psychic equivalent or variant or amnesia attack) (see figure 3, case 3, for a record taken during such an attack). Undoubtedly, brief attacks of this type are at times mistaken for petit mal. However, when they are accompanied in the electroencephalogram by a focal cortical abnormality, their true nature becomes apparent, if the interpretation used in this paper is correct.

Focal Cortical Seizures: Twenty-eight patients were regarded as having attacks the clinical pattern of which suggested a focal cortical origin. The electroencephalograms of 75 per cent (21 patients) showed a relatively localized unilateral abnormality, and those of 2 patients with clinically focal seizures, bilaterally synchronous sharp waves. The records of 5 patients showed a slight diffuse disturbance. This information, based on localization studies, indicated that the majority (75 per cent) of the patients with focal clinical seizures had a specific type of electroencephalogram. Classification, however, was impossible on the basis of the form and pattern of the waves alone, for individual subjects presented a wide variation and intermittent fluctuation in these characteristics when the activity increased. Patients with focal seizures of this kind frequently had a history of psychomotor attacks, "psychic equivalent or variant" states, episodes of "amnesia" or grand mal seizures; in addition their attacks had a progressive march, and at times a distinctive aura. In fact, some patients, at one time or another, had all these forms of clinical seizures, and hence, localization of the abnormality was the method of choice in classification of their disorder.

Petit Mal Attacks: Nineteen patients had what were clinically called petit mal attacks. On the basis of studies between clinical seizures, the electroencephalogram of 1 of these patients indicated a definite localized cortical disturbance (and, as previously mentioned, the condition

should therefore probably not be classified as petit mal); 12 patients presented activity of the bilaterally synchronous type; 4, slight diffuse abnormality, and 2, normal electroencephalograms. Only 3 of these patients had petit mal without a history of grand mal seizures as well. These 3 patients showed bilaterally synchronous subclinical activity of the 3 per second type.

"Psychomotor" Attacks, "Psychic Variant or Equivalent" states and "Amnesia": Thirty-four patients gave a history of attacks of this type. Twelve had focal cortical abnormality in the electroencephalogram; 15 bilaterally synchronous activity, and 7, a diffuse disturbance or a normal electroencephalogram.

Grand Mal Attacks: There were 86 patients with a history of grand mal seizures. As a subclinical phenomenon, 24 subjects showed a localized cortical disturbance, 30, a bilaterally synchronous abnormality and 32, either a slight diffuse change or a normal electroencephalogram.

Comment.—The following observations appear justified on the basis of the preceding data:

When the form of clinical seizure is known, one may make certain limited predictions as to the type of electroencephalogram that will be found on the basis of localization studies. For instance, in the majority of patients (75 per cent) clinical focal cortical seizures were associated with a localized cortical abnormality in the electroencephalogram.

In the presence of a history of petit mal attacks, the abnormality was almost always of the bilaterally synchronous type (suggesting a deep origin) when an active subclinical discharge was present (12 of 19 patients with petit mal, 6 of the 19 patients showing relatively no abnormal high voltage potentials at the time of study).

In the case of psychomotor attacks or grand mal clinical seizures no predictions could be made concerning the type of electroencephalogram (from the standpoint of localization) that would be associated, for all types of electroencephalographic patterns, unilateral localized cortical, bilaterally synchronous, diffuse and normal, were well represented.

RELATION BETWEEN LOCATION OF DISCHARGE AND TYPE OF CLINICAL SEIZURE

Clinical Seizures Associated with a Localized Unilateral Cortical Type of Abnormality (30 patients).—Seventy per cent (21) of the patients who had electroencephalographic patterns of this type gave a clinical history of focal epilepsy. For 53 per cent (16) of these patients a pathologic cortical lesion was demonstrated by air studies, operation or autopsy, and in each patient

of 5 patients the slow rhythmic waves occurred frequently and for many seconds at a time. In the other records these discharges were infrequent and of shorter duration. However, it is believed that all these discharges were essentially the same as those described as "psychomotor" by Gibbs, Gibbs and Lennox [3b] (figs. 2, 6 and 7), although the waves were not always square topped. Such slow rhythms were especially likely to occur when the activity increased in intensity (voltage) and spread to involve a somewhat larger area of cortex (so long as it did not become generalized, as in a grand mal attack). In approximately 50 per cent of the patients presenting this phenomenon (localized unilateral rhythmic discharges of 3 to 6 per second waves), the discharge was brought about by hyperventilation. In the others it

per second. At the onset of the clinical attack the random waves were replaced by higher voltage smooth potentials at 3 to 7 per second, as shown in figure 6. During the period of high voltage discharge, and for a short period thereafter, the patient became confused and out of contact and attempted to pull the electrodes off his head. He had what could be termed a "psychomotor" attack. It is interesting that his clinical manifestations were unlike his usual seizures, which as a rule consisted of a visual aura, at times followed by a grand mal convulsion. In the episode described the temporal lobe, as well as the occipitoparietal region, was involved, and some mirror activity appeared in the opposite hemisphere.

Another patient had a subclinical localized cortical type of disturbance in the left temporal
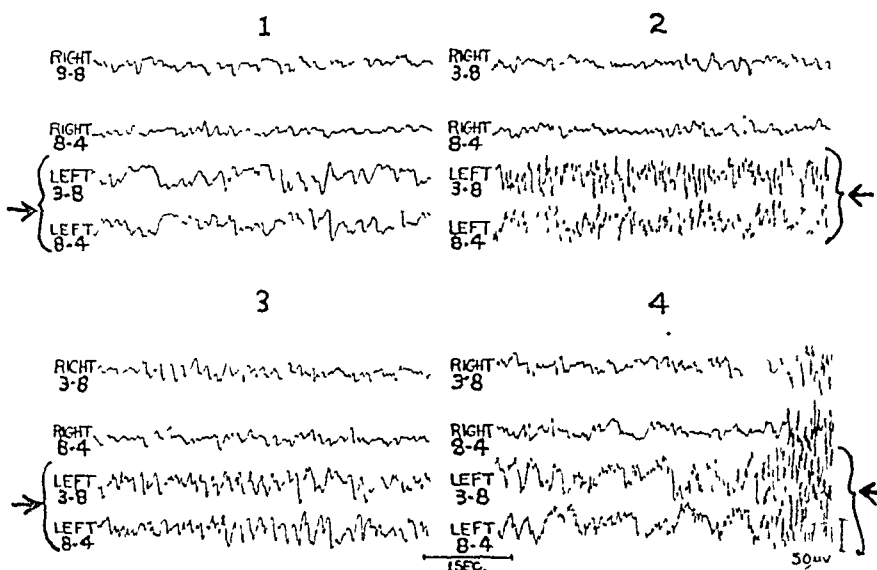
Fig. 7.—Records *1* to *4* show the evolution of a localized unilateral cortical discharge during the onset of a grand mal seizure. The abnormal (fast) activity became generalized, as will be seen in record *4*. At this point the patient mumbled incoherently and lost consciousness; the head turned to the right, and a few seconds later he had a grand mal tonic and clonic convulsion.

Before the onset of generalized fast activity, slow rhythms were present and alternated with fast (high frequency) wave discharges (see text).

Record *1* was taken one hundred and eight seconds before record *2* and record *2*, fifty-four seconds before record *3*. There was an interval of eighteen seconds between records *3* and *4*. The patient had hyperventilated for three and one-half minutes at the onset of tracing *4*.

occurred spontaneously. Examples of these slow wave patterns are shown in figures 2 (cases 1, 4, 6, 7 and 8), 6 and 7.

The rhythmic waves just described were all noted subclinically in patients who did not have a clinical seizure for at least twenty-four hours before or after the tracing had been taken.

In 1 patient similar 3 to 6 per second waves were recorded during a clinical attack. This subject, as a subclinical phenomenon, presented a localized unilateral cortical discharge of random waves (from the left occipitotemporal region), which at intervals became of higher voltage and rhythmic, with a frequency of 3 to 6

region, made up of random waves which at intervals, as in the other case, became rhythmic and of higher voltage, with a frequency of 3 to 6 per second. This patient had a sudden change in his cortical potentials during the taking of the tracing, as shown in figure 7. As will be seen, the random unilateral waves were replaced by rapid ones, which became intermittently rhythmic at 3 to 6 per second, and three seconds later high voltage fast waves spread over the entire head. Clinically the patient exhibited a fixed stare just preceding the appearance of the high voltage generalized fast waves; his head turned to the right, and he then had a grand mal seizure.

clinical attacks. An attempt to determine the significance of these observations, especially as concerns their "psychomotor" form of activity, is presented in this part of the paper. To begin with, the electroencephalographic aspects will be considered, and later these will be correlated with the clinical data.

"PSYCHOMOTOR" TYPE OF ELECTRICAL ACTIVITY

Gibbs and associates [3b] described their "psychomotor" activity as consisting of

... cortical action potentials which are of high voltage and slow frequency—from 3 to 6 per second. There are series of regular, square-topped waves with the normal rhythm of from 8 to 10 per second still present on the crest. . . . At another period of the seizure the waves, though still of high voltage, are more irregular and without the crenated crests.

Similar activity occurring as a subclinical phenomenon is also referred to as "psychomotor."

were seen. This was also found to be true by Finley and Dynes.[16] The waves referred to as square topped (figs. 2 to 4, 6 and 7) usually alternated with smooth or sharp forms, even in tracings from patients with the most severe "psychomotor" clinical manifestations.

Electrically one such discharge seemed essentially the same as another. In view of this nonspecificity in the changes in slow potential, all high voltage 3 to 6 per second rhythmic wave discharges were classed as "psychomotor" even though some of them were of short duration and occurred only occasionally in a record. This was done purely to facilitate analysis, and it is believed that in the future it would be preferable to drop the term "psychomotor" in referring to electroencephalographic patterns.

In the analysis to follow, slow wave patterns will be considered under three headings, according to their localization in the brain.
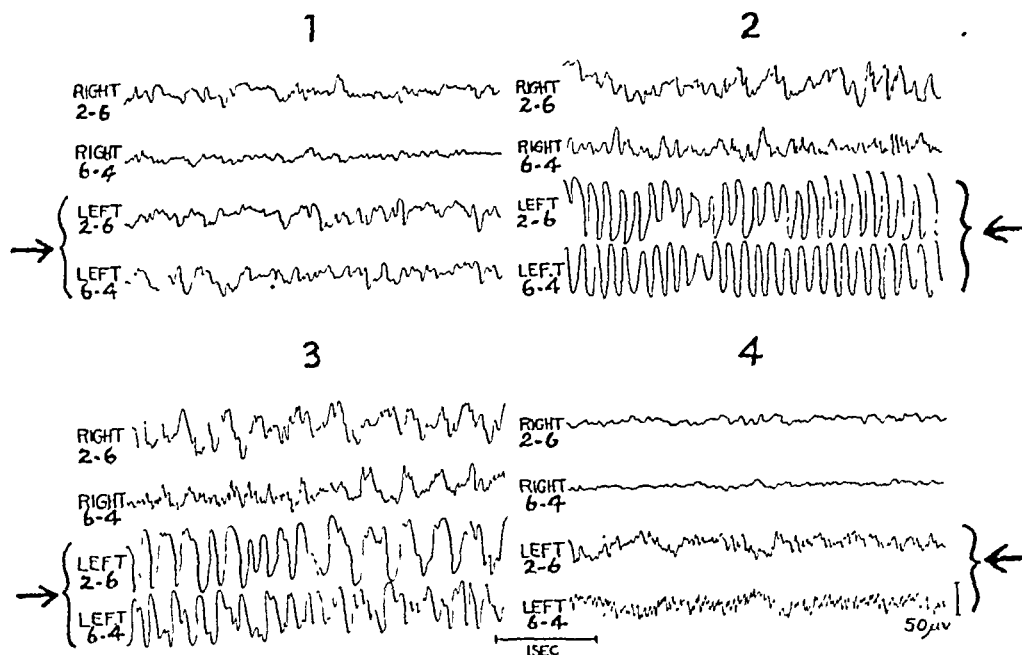
Fig. 6.—Unilateral localized cortical abnormality, illustrating the evolution of the discharge during a clinical attack. Tracings were taken simultaneously from homologous areas on the two sides of the head. The record was taken six minutes before (1), during (2 and 3) and four minutes after (4) a "psychomotor" clinical seizure, in which the patient showed mental confusion and uncontrolled movements. The lesion in this case was an area of cortical atrophy in the left occipitotemporal region, demonstrated by air encephalogram. The patient had frequent visual auras and occasional grand mal episodes. When his localized discharge increased in intensity, as shown in the present tracings, it involved the left occipitotemporoparietal region and gave rise to mirror activity in the opposite hemisphere. The same slow pattern, when less intense, was associated with a visual aura alone on one occasion. The waves are smooth topped during the height of the "psychomotor" clinical and electrical disturbance and later show considerable variation in form, as do most of the 3 to 6 per second potentials in other figures in this paper (see text).

In the records studied in the present series, 3 to 6 per second rhythms were a common feature (see percentages cited later). It was not possible, however, to say which of these slow rhythmic disturbances should be classed as "psychomotor." No truly square-topped waves, of the "textbook" form of Gibbs and Gibbs,[21]

Localized Unilateral Cortical Disturbances.—In studying the discharges of localized cortical type, it was found that the abnormal waves occurred at random, as described by Jasper and Kershman.[18] However, in over 50 per cent of the 30 patients showing this form of abnormality it was noted that the random potentials were replaced at some time during the recording by rhythmic trains of high voltage slow waves, with a frequency of 3 to 6 per second. In the records

21. Gibbs, F. A., and Gibbs, E. L.: Atlas of Electroencephalography, Cambridge, Mass., Lew A. Cummings Co., 1941. p. 16.

variant" states or episodes of "amnesia." Nine of these patients had subclinical 3 to 6 per second rhythmic wave patterns in their electroencephalograms, and 3 of them did not show such changes. It will be remembered that at least 15 (50 per cent) of the 30 patients with localized cortical activity had 3 to 6 per second discharges (figs. 2, 6 and 7). Therefore 6 patients had these electrical disturbances without any history of psychomotor or variant clinical seizures. In the electroencephalograms of 5 patients (as previously mentioned) the psychomotor electrical pattern was a prominent feature in contradistinction to those showing only brief trains of rhythmic 3 to 6 per second waves. Four of these 5 patients gave a history of clinical symptoms of a more pronounced "psychomotor" nature than any of the other patients with similar episodes.

For the 9 epileptic patients who had both electrical and clinical "psychomotor" patterns, the location of the abnormal discharges was as follows: left temporal region, 4 patients; left frontal lobe, 1 patient, and left parietal or occipital lobe in the region of the left angular gyrus, 4 patients. Of the patients with rhythmic 3 to 6 per second waves, but without clinical "psychomotor" symptoms, the disturbance was localized as follows: left temporal region, 1 patient; right frontal region, 1 patient; left parietal region, 2 patients; right parietal region, 1 patient, and left occipital region, 1 patient.

Psychomotor Seizures and Bilaterally Synchronous Sharp Waves (B 2 Activity).—As previously stated, over 65 per cent (9) of the 14 patients with electroencephalograms showing bilaterally synchronous sharp waves over the temporal lobes had rhythmic wave discharges at a rate of 3 to 6 per second at some time during the recording. Eight of the 14 patients (with bilateral sharp wave activity) had a history of "psychomotor" clinical attacks, and 5 of these 8 patients had 3 to 6 per second rhythmic potential changes as well. Four patients with 3 to 6 per second waves had no history of "psychomotor" clinical attacks, and the slow rhythmic patterns were somewhat less prominent in these persons.

Psychomotor Seizures and Three per Second Wave (B 3) and Wave and Spike (B 1 and 3) Activity.—Of the 7 patients with subclinical 3 per second wave and spike patterns, only 1 gave a history of "psychomotor" clinical seizures. Six patients, however, of the 13 patients from whom bilateral 3 per second waves were obtained had such clinical episodes. It is debatable whether 3 per second smooth waves should be regarded as "psychomotor" in type.

It is true, however, that the smooth waves frequently changed from moment to moment to the square-topped form typical of the "psychomotor" patterns, as shown by Gibbs and associates (fig. 3, tracing 18 [3b]) and illustrated here (fig. 3, case 5). The "psychomotor" symptoms presented by most of these subjects could be described as of the behavior problem type or as periods of mental dulness.

In the group under discussion, square-topped 3 per second waves, as shown in figure 3, case 5 and figure 4, *3*, were as common in patients with "psychomotor" clinical seizures as in those with no history of them (see "Comment" and "Summary" for further consideration of the significance of these observations.)

POSSIBLE SIGNIFICANCE OF FREQUENCY IN ELECTROENCEPHALOGRAPHIC DISTURBANCES

Partly because slow rhythmic waves accompany psychomotor seizures and fast potentials grand mal attacks, it has been suggested that "high frequencies produce overactivity and slow frequencies underactivity." [3b] If this observation is correct, it would have a fundamental bearing on the interpretation of the electroencephalogram and therefore deserves careful consideration.

It is well known that when the abnormal activity in any case of epilepsy becomes generalized and results in a grand mal attack, the onset of the convulsion is frequently accompanied by high voltage fast waves (as described by Gibbs, Gibbs and Lennox [3b]). But at this stage of the episode the patient usually loses consciousness. In other words, the "high frequency" waves are accompanied by, or produce, underactivity (loss of consciousness), rather than overactivity, as suggested in the preceding paragraph.

Leading up to this stage in an epileptic seizure, it is not uncommon to see bursts of high voltage fast waves alternating with slow rhythmic potentials at 3 to 6 per second (fig. 7). To explain this phenomenon on the basis of the hypothesis under discussion, overactivity would have to alternate with underactivity every few seconds. No evidence to support this assumption has been found.

It will also be remembered that during the violent clonic phase of a convulsion slow rhythmic high voltage waves are a common feature of the electroencephalogram. This is also true during a "psychomotor" seizure, in which clouding of consciousness (underactivity) may be accompanied by rage or excessive activity in the motor sphere (as in the case illustrated in figure 6). It seems that in both these states it

The clinical significance of these observations will be considered later.

Bilaterally Synchronous Cortical Activity.— In over 65 per cent of patients (9) presenting bilaterally synchronous potentials of the sharp wave (B 2) type, particularly over the temporal lobes, rhythmic trains of high voltage waves at 3 to 6 per second occurred at some time during the taking of the electroencephalogram. The patterns formed were similar to those called "psychomotor" by Gibbs, Gibbs and Lennox.[3b] The tracing in figure 3, case 3, illustrates such activity.

Three per Second Wave and Three per Second Wave and Spike Pattern: In the records of patients with bilaterally synchronous 3 per second wave and spike patterns it is not uncommon (2 of 7 patients) to see trains of 3 per second smooth or square-topped waves as a subclinical phenomenon (fig. 4, 3). There does not appear to be any fundamental difference between these 3 per second waves (especially the square-topped forms) and the rhythms described as "psychomotor" by Gibbs, Gibbs and Lennox (fig. 3, tracing 18[3b]). The same may be said of the 3 per second smooth and square-topped waves seen in the electroencephalograms classified as showing 3 per second wave activity (fig. 3, case 5). All such disturbances have therefore been classified as being of "psychomotor" type.

Comment.—From the observations just stated, it appears that "psychomotor" (3 to 6 per second wave) patterns are common (present in the records of over 50 per cent of patients with high voltage epileptic disturbances) and may occur in a localized unilateral cortical discharge, in one arising deep in the brain in the neighborhood of the temporal lobes or in one apparently originating near the midline. Such patterns, therefore, have no specific location of origin in the brain. Localization of these potential changes, then, would be one method of classifying them.

POSSIBLE CLINICAL SIGNIFICANCE OF CERTAIN
WAVE PATTERNS IN THE ELECTRO-
ENCEPHALOGRAM

Exception has been taken to the use of clinical terms, such as "psychomotor," petit mal and grand mal, to describe certain patterns in the electroencephalogram.[22] This criticism is based on the fact that similar electrical disturbances are seen as a subclinical phenomenon in patients who never had clinical seizures of the type implied by the name used to describe the changes in the electroencephalogram.

The important observation of Gibbs and associates[3b] remains true, however, namely, that certain electroencephalographic patterns frequently occur during particular types of clinical seizures. There must be some explanation for these phenomena. A hypothesis is advanced in the "Summary" which may explain their association.

In the next paragraph is considered the question of what clinical manifestations may be included under the term "psychomotor." An attempt is then made to determine what relation exists between "psychomotor" subclinical discharges and "psychomotor" clinical seizures. The significance of the observations will be left for consideration in the final discussion, in which the possible significance of electroencephalographic patterns associated with petit mal and with grand mal seizures will also be analyzed.

"Psychomotor" Clinical Seizures.—The clinical seizures associated with this form of electrical activity, it will be recalled, were described by Gibbs, Gibbs and Lennox[3b] as of "psychomotor," "psychic variant or equivalent" or "amnesia" type.

Now it appears, if my interpretation is correct, that not a specific type of epileptic seizure, but a wide variety of epileptic manifestations, is represented by these clinical terms.

In the first place, many episodes termed "psychomotor" are in reality expressions of automatism, as pointed out by Penfield and Erickson.[11] Such attacks are apparently usually (but not necessarily always) release phenomena, either during (ictal) or after (postictal) an epileptic discharge.

In addition to episodes of automatism, it seems that certain psychic seizures usually regarded as arising in the temporal lobes, attacks of sensory aphasia and, in fact, any seizure (apart from typical petit mal) accompanied by mental confusion (transitory or otherwise) that is not immediately associated with a clonic or generalized convulsion must be included with the "psychic variant or equivalent" or the "amnesia" type. Such an interpretation has been used in naming and classifying seizures in this paper, and as a result all such clinical episodes are referred to at times as "psychomotor," for the sake of convenience.

CORRELATION OF CLINICAL MANIFESTATIONS AND
LOCATION OF "PSYCHOMOTOR" DISTURBANCES

"Psychomotor" Clinical Seizures and Localized Unilateral Cortical Discharges.—Of the 30 patients with cortical discharges of this type in the electroencephalogram, 12 gave a history of "psychomotor" attacks, "psychic equivalent or

22. Finley.[17] Finley and Dynes.[16] Jasper and Kershman.[4]

parently usually made up of high frequency discharges from individual neurons. The separate waves are due to the summation effect of a large number of these cells firing simultaneously, but apparently at high frequencies. The term "slow frequency discharge" in this sense is therefore misleading, for the individual neurons in such a "slow frequency" disturbance may be firing at as high rates as, or at higher rates than, those in a so-called fast wave discharge. ·

The observations just reported pertain to the abnormal high voltage electrical activity in the records of epileptic patients, and it is not disputed that in a nonepileptic discharge an increase or a decrease in frequency of the cortical potentials over that usually regarded as normal might produce the effects suggested by Gibbs.[21]

SYNCHRONOUS AND ASYNCHRONOUS DISCHARGES ASSOCIATED WITH EPILEPSY

The nature of the nerve impulse discharges which go to make up the various abnormal waves that may be recorded from the brains of epileptic patients is of considerable interest.

Adrian and Matthews [24] originally suggested that the alpha rhythm (8 to 13 per second) normally seen in the electroencephalogram was the result of the synchronous discharge of large numbers of cells (firing at their normal frequency of 8 to 13 per second) in the region of the occipital lobes when these areas were at rest or were freed from the bombardment of visual afferent impulses when the eyes were closed. Jasper and Nichols[20] and Jasper and Kershman[4] extended this hypothesis to include the high voltage waves seen in the records of epileptic patients. One of the features of the electroencephalogram of such patients is the presence of recurring outbursts of large voltage waves, a phenomenon described by these authors as paroxysmal hypersynchrony.

Before the waves in epilepsy are considered in detail, it is perhaps well to consider what is meant by a synchronous as opposed to an asynchronous discharge. The example to be given deals only with a fast wave disturbance, in which each receptor contributes only one impulse to each wave in the discharge.

Figure 8, *1*, shows the type of disturbance which results when the gastrocnemius muscle (in a frog) is stretched with a steady tension. In this case the many receptors in the muscle send out impulses at different frequencies, and the resulting discharge is a low voltage asynchronous one. The same type of asynchronous discharge of impulses occurs each time the muscle is stretched (unless the period of stretch is brief, as in the case cited in the next paragraph). This is true, for instance, if tension is applied to the muscle intermittently (rhythmically) at a rate of 3 per second (each stretch lasting approximately one-third second). In this case one might argue that the activity occurs synchronously in each receptor and that the periods are synchronized with the pacemaker (at 3 per second). However, although the periods of activity are approximately the same for all receptors, the rate of discharge of impulses from each unit is different, and the resulting change in potential is the product of an asynchronous, and not a synchronous, discharge.

Now, if the muscle is stretched intermittently by a rapid vibrating stimulus (such as that from a tuning fork with a rate of, say, 128 per second), most of the individual stretch receptors fire off impulses at the same rate (at the frequency of the fork, each receptor usually contributing one impulse at each vibration), and thus a truly synchronous discharge occurs, which in this instance is composed of high voltage fast waves occurring in rhythmic fashion. Each wave in the illustration shown is of approximately the same duration as that from a single impulse (fig. 8) and varies in height (voltage) according to the number of impulses contributing. In the case just given, unlike that cited in the previous paragraph, the discharge of impulses, as well as the period of activity, from each receptor is synchronized with the discharges from the other receptors and, also, with the tuning fork (pacemaker).

In the electroencephalogram associated with epilepsy, as mentioned previously, one sees occasional rhythmic series of high voltage fast waves. These are apparently true synchronous discharges, similar to the potential shown in figure 8. Individual high voltage spikes or multiple spikes are also apparently due to the synchronous discharge from a number of nerve cells and are therefore presumably the product of hypersynchrony.

Whether such an explanation, however, as implied by Jasper's[25] term "paroxysmal hypersynchrony," is sufficiently explanatory when applied to epileptic discharges in general appears to depend partly on the nature of the slow potential changes in the cortex. With the exception of "spikes" and certain fast waves, the

23. Gibbs, F. A.: Interpretation of the Electroencephalogram, J. Psychol. **4**:365-382, 1937.
24. (*a*) Adrian, E. D., and Matthews, B. H. C.: Interpretation of Potential Waves in Cortex, J. Physiol. **88**:440-471, 1934; (*b*) The Berger Rhythm: Potential Changes from the Occipital Lobes in Man, Brain **57**: 355-385, 1934.

25. Jasper and Kershman[4]   Jasper and Nichols.[20]

might be argued that slow frequencies (waves) produce, or are associated with, overactivity, rather than underactivity.

Why high frequency potentials often accompany the onset of a grand mal seizure is not definitely established. It appears, however, that when the disturbance spreads rapidly, as in such a seizure, the cortical cells may behave in one of two ways: (a) They may fire off at relatively high frequencies and independently (at different rates), producing an asynchronous fast wave discharge (as shown in figures 7 and 8), or (b) they may discharge rhythmically and at high frequencies, apparently in a truly synchronous manner (comparable to that shown in figure 8).

of the cortex (during the clonic phase of the attack) may show rhythmic periods of activity and rest, so that masses of cells fire simultaneously and then become quiescent; i. e., the rhythm (frequency of the waves) slows.

This tendency for a slow rhythm to appear seems characteristic of most abnormal electrical disturbances in the brain of epileptic patients when large masses of cells are involved in intense activity for any appreciable length of time. Such slow frequency waves seem to produce underactivity (in an epileptic attack), but only in the sense that physiologic function is disturbed when a large portion of the brain is taken over by excessive abnormal activity.
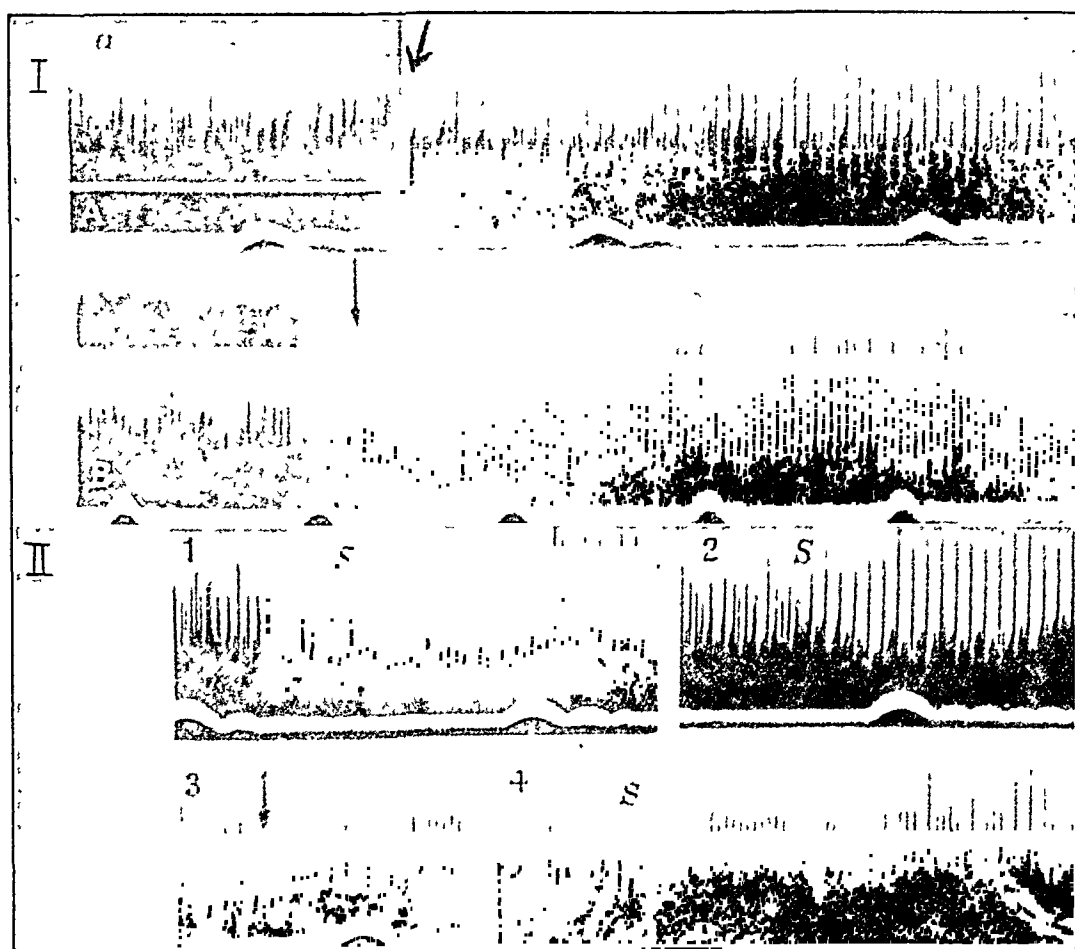
Fig. 8.—I A, insert a, and I B, to the left of the arrow, are examples of asynchronous discharges of impulses in nerve when steady tension is applied to the gastrocnemius muscle of the frog. The insert in I B shows the base line of the record before stretch was applied.

In I A and B, at the arrow in each case, are seen synchronous discharges of impulses from the stretch receptors when a tuning fork is applied to a string attached to the tendon of the gastrocnemius muscle.

In II, tracing 4 at S shows the type of waves produced by individual nerve impulses from a single receptor (in a frog's toe muscle). Tracing 1 and 2 at S show the type of waves resulting from the synchronous response of two receptors (see original article for further explanation). In each case the waves are of approximately the same duration regardless of the number of units involved and vary only in amplitude. This is in contrast to the waves in epilepsy, which usually become "slow" when large numbers of units discharge simultaneously (see text). The time marker indicates one-fifth second intervals (from Echlin, F., and Fessard, A.: J. Physiol. 93:312-334, 1938).

The rate of this discharge may be the same as the normal alpha or beta rhythm or may occur at a higher frequency. Other aspects of this hypothesis are discussed in more detail later.

After this stage in the evolution of the disturbance in a grand mal convulsion, large areas

In addition to the aforementioned observations, it should be noted that when one speaks of slow frequencies, one is referring to discharges of slow waves and not to the frequency of nerve impulses. As pointed out later, these slow potentials (in epileptic patients) are ap-

demonstrated by Jasper and Kershman,[4] Penfield and Erickson [11] and others).

The possible significance of the various wave forms and electrical patterns, the frequency of the waves seen in the electroencephalogram and certain physiologic mechanisms concerned in the production of these abnormal potentials will now be discussed briefly.

FOCAL OR LOCAL NATURE OF EPILEPTIC DISCHARGES

With regard to the evidence in favor of the localized origin of the different disturbances, one may consult the paper by Jasper and Kershman [4] and the recent book by Penfield and Erickson.[11]

There is no doubt that the attacks of a large number of epileptic subjects (30 per cent in the present selected series) have a localized unilateral cortical origin, as demonstrated by Golla, Graham and Walter [7]; Jasper and Hawke [8]; Case and Bucy [10]; Jasper and Kershman [4]; Penfield and Erickson [11]; Gibbs, Merritt and Gibbs,[12] and others. Evidence that the bilateral synchronous waves (35 per cent of patients in this study) originate in, or are controlled from, a relatively localized area, deep in the brain, either near the midline or in the neighborhood of one of the temporal lobes, has been discussed at length by Jasper and Kershman [4] and Penfield and Erickson,[11] and I shall not repeat it here, except to say that the electrical and clinical observations in this study are in keeping with the hypothesis expressed by these authors.

There is evidence (page 275) that the slight diffuse disturbance noted in 15 per cent of the patients (with abnormality relatively quiescent at the time of study) may occasionally be due to a feebly discharging area deep in the brain. Such an abnormality might, therefore, at times also be regarded as having a relatively local origin.

As already mentioned, the records of 20 per cent of the patients were considered normal. The epileptic discharges in these patients were, therefore, inactive at the time of study, and no conclusions can be drawn regarding the source of their seizures except from clinical criteria.

In summary, it may be stated that the observations are in keeping with the hypothesis that most epileptic discharges (over 65 per cent) apparently arise as relatively local or focal disturbances in the brain and that localization of these changes in potential by means of the electroencephalogram serves as one basis for classification of the epilepsies.

POSSIBLE SIGNIFICANCE OF WAVE FORMS AND PATTERNS IN THE ELECTROENCEPHALOGRAM

In the body of the paper, the observations concerned with the electrical and clinical patterns of so-called psychomotor, petit mal and grand mal were reported and commented on. These observations will be reviewed and discussed here.

Gibbs, Davis and Lennox [2] and Gibbs, Gibbs and Lennox [3b] were the first to report that 3 per second wave and spike patterns occurred during petit mal attacks; 3 to 6 per second, frequently square-topped, potentials, during "psychomotor" episodes, "psychic variant or equivalent" states or seizures of "amnesia," and high voltage fast waves, during episodes of grand mal.

It should be reemphasized here that the present report (as well as the much more extensive one of Jasper and Kershman [4]) is based largely on a study of electroencephalograms taken between seizures, and hence the results do not conflict with the important observations of Gibbs and associates,[29] during clinical attacks. The use of clinical terms like petit mal, psychomotor and grand mal to describe subclinical electrical patterns, however, is perhaps misleading, since such abnormalities occur in the electroencephalograms of patients who do not have attacks of the type implied, as demonstrated in this series and by Jasper and Kershman,[4] Finley and Dynes,[16] Finley [17] and others.

So-Called Psychomotor Clinical and Electrical Patterns.—Slow rhythmic high voltage waves at 3 to 6 per second were present at intervals in the records of over 50 per cent of the epileptic patients from whom high voltage abnormal waves were recorded. These slow rhythmic patterns were found in discharges arising from a unilateral localized area in the cortex, as well as in disturbances originating deep in the region of a temporal lobe or apparently deep near the midline of the brain (figs. 2 and 4).

Electrically there did not seem to be any fundamental difference between one of these slow rhythmic disturbances and another. The shape of the individual waves in most cases fluctuated from moment to moment from a sharp to a smooth or a square-topped form. This fluctuation in form appeared to depend chiefly on the changing intensity of the discharge, on its position in the brain and its relation to the recording elec-

---

29. Gibbs, Davis and Lennox.[2] Gibbs, Gibbs and Lennox.[3b]

majority of the waves recorded from the cortex of epileptic patients are slow. There is some doubt concerning the origin of these slow waves. Gerard and Libet [26] apparently concluded that individual nerve cells may give rise to slow electrical potentials and that synchronous action of a group of such cells may produce a slow wave which is a close replica of that from a single cell except that it is of greater voltage. Adrian and Matthews [24a] pointed out that the activity of cortical neurons consists of a series of brief pulsations. The existence of slow waves in experimental epilepsy, they stated, implies asynchronous discharges in the different parts of the area which contributes to the potential gradient. From this point of view, the slow waves are summation effects of an excessive discharge of a large number of neurons firing asynchronously (at different frequencies), and the response of each unit bears no resemblance to them. Adrian and Matthews [24a] stated, however, that there must be a general agreement in the periods of rest and activity over considerable areas of cortex, although the neurons in these areas are not pulsating in phase. In epileptic human subjects the presence of smaller waves, which are often superimposed on the crest of the slow potentials, favors this theory of asynchronous firing of the individual units which go to make up the slow waves (figs. 2 and 4).

These observations are supported by more recent ones, in which Adrian and Moruzzi [27] (recording from single fibers in the pyramidal tracts of animals) demonstrated that the cortical waves in experimental epilepsy are usually summation effects from neurons firing impulses asynchronously, at frequencies sometimes as high as 500 to 1,000 per second.

If my interpretation of the observations of Adrian and his co-workers [28] is accurate, the term paroxysmal hypersynchrony (although of course correct) is not sufficiently explanatory of the physiologic mechanism concerned in the production of most of the recurring or paroxysmal high voltage slow potentials which can be recorded from the brains of epileptic patients.

It is true that the periods of abnormal activity in the various neurons (contributing to a slow potential) may occur synchronously with one another and with the so-called pacemaker (show periodic simultaneous intervals of activity and

rest, i. e., hypersynchrony, as suggested by Jasper and associates [25]) but the resulting trains of nerve impulses in the separate axons apparently occur at different frequencies (as in the case of the activity of muscle receptors to relatively prolonged stretch), and the composite discharge of impulses (which presumably also contributes to the slow wave) is therefore asynchronous.

COMMENT

Although this study is based on a small number of patients (100), certain observations appear justified.

In only a little over 65 per cent of the patients with convulsive seizures studied were paroxysmal high voltage waves present in the tracings taken between clinical attacks. The remaining patients had either a normal electroencephalogram (20 per cent) or a slight diffuse abnormality, consisting chiefly of low voltage waves (15 per cent). With the exception, perhaps, of bilaterally synchronous 3 per second wave and spike discharges, the subclinical electrical abnormalities recorded could not be regarded as specific for epilepsy, and a diagnosis of epilepsy on the basis of the electroencephalogram alone was therefore rarely felt to be justified.

Probably the chief value of the present investigation is that it corroborates in large part the observations of Jasper and Kershman [4] that electroencephalograms taken from epileptic patients between seizures may be classified on the basis of localization studies into four groups, namely, (1) localized unilateral cortical abnormalities, (2) bilaterally synchronous abnormalities, (3) diffuse abnormalities and normal electroencephalograms.

The fact that convulsive states may be classified with considerable accuracy according to localization studies, in this manner, is of value from a clinical standpoint and, in addition, throws light on certain aspects of the physiologic mechanism of epilepsy. The observations reported are in keeping with the hypothesis that the discharge in most patients with epilepsy (over 65 per cent) may originate as a relatively focal or local disturbance and then, under certain circumstances, spread to other regions of the brain. The clinical manifestations resulting from such abnormal or excessive electrical activity appeared to depend largely on the function of the areas of the brain involved or influenced (and the intensity of the discharge). In other words, a correlation was found to exist between the patient's type of epileptic seizure and the location of his abnormal discharge (as

26. Gerard, R. W., and Libet, B.: On the Unison of Neurone Beats, in Ozoro de Almeida, A., and Ozorio de Almeida, M.: Livro de Homenagem, Rio de Janeiro, Brazil, 1939.

27. Adrian, E. D., and Moruzzi, S.: Impulses in Pyramidal Tract, J. Physiol. 97:153-199, 1939.

28. Adrian and Matthews.[24] Adrian and Moruzzi.[27]

others. The few patients whom my associates and I studied during clinical attacks showed typical 3 per second waves and spikes.

Patients with such electrical patterns (subclinical or clinical) apparently have essentially the same type of epilepsy (with respect to the location of the discharge) regardless of whether or not they have a history of clinical petit mal attacks, for in all patients presenting such bilaterally synchronous potentials the origin of the disturbance appears to be in a deep central midline area. When the discharge in such a patient is of a certain intensity, he may become irritable and present the picture of a "behavior problem." When the voltage of the waves shows a decided increase for a brief period, a petit mal seizure may result. On the other hand, if the electrical activity becomes more intense still and is prolonged, a generalized grand mal episode without localizing features results (as pointed out by Jasper and Kershman[4]). Certain persons with subclinical 3 per second waves and spikes have only grand mal attacks, presumably because when the electrical activity increases in intensity sufficiently to produce clinical symptoms, it always does so in an intense and persistent manner. Theoretically, however, these persons could have a petit mal attack if at any time a brief intense discharge should occur.

All these clinical seizures are characterized by their generalized nature, and there is nothing in their clinical pattern to suggest that they may have originated in a localized area of the cerebral cortex. This is in keeping with the hypothesis of the origin of the activity in a deep central midline area (as indicated by the work of Jasper and Penfield and associates[11]).

Such a hypothesis suggests that although a 3 per second wave and spike pattern (in an epileptic patient) does not always mean that he has petit mal epilepsy, it indicates that he has a specific form of epilepsy with respect to the location of the abnormality, and hence the observation of Gibbs, Davis and Lennox[2] is fundamental if one agrees to disagree over terminology.

So-Called Grand Mal Activity.—In the electroencephalograms studied in this investigation it was not possible to determine whether the presence of high voltage fast waves between clinical attacks indicated that the patient had grand mal epilepsy. High voltage potentials at 15 to 50 per second occurred as a subclinical phenomenon in over 5 per cent of the records, but little significance could be attached to this observation since 86 per cent of all the patients included in the series gave a history of grand mal seizures. That subclinical high voltage fast waves are not specific for any form of epileptic attack is, however, indicated by the work of Finley,[17] who reported their presence to be more frequent in association with neurosyphilis and affective psychoses than with grand mal.

This, of course, does not invalidate the observation of Gibbs and his associates that actual clinical grand mal seizures are accompanied by fast potentials of high voltage. This was true for the 3 patients from whom we obtained tracings during a major convulsion.

SUMMARY

The electroencephalograms of 100 patients with recurrent epileptic seizures could be classified with considerable accuracy according to the classification of Jasper and Kershman,[1] which is based on the localization of the discharge. The results of the study are in keeping with the hypothesis that most epileptic discharges (over 65 per cent) apparently arise as local or focal disturbances in the brain. There appears to be a distinct correlation between the location of the electrical abnormality and the type of clinical seizure suffered by the patient, as described by Jasper and Kershman.[4]

It appears that high voltage abnormal waves in the electroencephalograms of epileptic patients commonly (in over 50 per cent of the 65 patients from whom such waves were recorded) take on a rhythmic 3 to 6 per second pattern for brief, or more prolonged, periods. This seems to hold true regardless of whether the waves originate in a focal cortical discharge or in a deeper disturbance. When these 3 to 6 per second slow potentials are of medium voltage and occur relatively infrequently, or are confined to "silent" areas of the brain, there may be no associated symptoms. If they are of high voltage and involve large areas or regions, such as the left temporal lobe, there may result a variety of manifestations, such as "psychomotor" attacks, "psychic equivalent or variant" states or of episodes of "amnesia," as described by Gibbs, Gibbs and Lennox.[3b] At times an apparently similar type of electrical abnormality is seen in the records of behavior problem children, as reported by Jasper and associates[30] or is associated with periods of mental dulness, as observed by Putnam and Merritt.[31] It seems that the electrical pattern or abnormality in all epileptic patients with this slow rhythmic type of disturbance is essentially the same, but is nonspecific, and that the variability in the associated symptoms depends largely on the location and intensity of the discharge.

trodes and on the degree of synchronization of the units participating. That the potentials in certain instances at intervals presented a square top did not in itself appear a sufficient criterion to warrant the separation of these records from the others, into a so-called psychomotor group. Actually, square-topped forms were almost as common in the records of patients with no history of psychomotor seizures as in those of patients with such seizures.

In the present study, all high voltage 3 to 6 per second rhythmic slow potentials have been classified as "psychomotor" disturbances to facilitate analysis. This seems justified because of the essential similarity of these abnormalities, but it is suggested that in the future it might be preferable to drop the term "psychomotor" in describing these electrical patterns.

Only about 55 per cent of patients with high voltage rhythmic 3 to 6 per second waves had what might be termed clinical attacks of "psychomotor," "psychic variant or equivalent" or "amnesia" type.[3b] All these subjects had other forms of clinical epileptic seizures, in addition to their "psychomotor" episodes. From this it is evident that 3 to 6 per second waves of the "psychomotor" type are common in a wide variety of epileptic discharges, that they have no specific site of origin in the brain and that they do not necessarily mean that a patient will have psychomotor clinical seizures. In other words, they are not specific for this type of attack. This is in keeping with the fact that they are seen during sleep and anesthesia and in animals, as well as in persons with no history of epilepsy, as reported by Finley and Dynes.[16]

The clinical manifestations which accompanied 3 to 6 per second waves varied widely in the cases presented in this paper. Even those episodes classified as psychomotor attacks, psychic equivalent or variant states or amnesia have not conformed to any specific pattern. In fact, it was felt necessary to include under this type all attacks (other than true petit mal) in which the patient showed a clouding of consciousness (transitory or otherwise), providing there was not an accompanying grand mal or jacksonian motor or sensory seizure. The reason for this variation in symptoms associated with 3 to 6 per second waves appeared to depend largely on the location and intensity of the electrical disturbance.

It is apparent that in an epileptic subject abnormal electrical activity of the slow rhythmic type would disturb physiologic function in the cells participating if its intensity was sufficiently great. If the area of brain involved in such a disturbance was large enough or was concerned with higher intellectual function (such as the left temporal lobe), it is easy to see how clouding of consciousness (psychomotor variant, psychic equivalent or variant or amnesia) might occur unless unconsciousness supervened. Similar activity confined to a more "silent" area, however, such as the right frontal or right temporal lobe, might give rise to few or no clinical manifestations unless the disturbance spread, when a generalized seizure, with or without a "psychomotor" element, might be the outcome.

Many instances of "psychomotor" clinical attacks arising from unilateral localized cortical areas and from a focus deep in the brain have been given in the body of the paper. All these "psychomotor" clinical episodes differed from one another. Perhaps the one thing in common to all the episodes included under this heading was the occurrence of some disturbance of consciousness, transitory or otherwise.

There are other examples of the wide variation of manifestations that may accompany these slow rhythmic waves. Jasper and associates,[30] for instance, reported bilateral rhythmic slow potentials in the records of a group of behavior problem children, and Putnam and Merritt [31] observed similar wave patterns for patients showing only periods of mental dulness. It appears that the location and the intensity of the disturbance must have played at least a considerable part in determining the variability in the symptoms presented by these different subjects.

Although it seems that rhythmic 3 to 6 per second waves may from time to time appear in almost any high voltage epileptic discharge, it remains to be explained why only a few people have these rhythmic potentials as a prominent feature of their electroencephalograms. It was the few persons with such an electrical pattern in this study who had most pronounced "psychomotor" symptoms, an association pointed out by Gibbs, Gibbs and Lennox.[3b] This was particularly true when the electrical abnormality involved the left temporal lobe or arose deep in the brain.

The So-Called Petit Mal Type of Disturbance.—The 3 per second wave and spike pattern is apparently the electrical abnormality usually, if not always, present during petit mal seizures, as originally reported by Gibbs, Davis and Lennox [2] and corroborated by Jasper and Kershman [4] and

30. Jasper, H. H.; Solomon, P., and Bradley, C.: Electroencephalographic Analyses of Behavior Problem Children, Am. J. Psychiat. 95:631-658, 1938.

31. Putnam, T. J., and Merritt, H. H.: Dulness as Epileptic Equivalent, Arch. Neurol. & Psychiat. 45: 797-813 (May) 1941.

THE ELECTROENCEPHALOGRAM ASSOCIATED WITH CHRONIC ALCOHOLISM, ALCOHOLIC PSYCHOSIS AND ALCOHOLIC CONVULSIONS

MILTON GREENBLATT, M.D.; SIDNEY LEVIN, M.D., AND FERRUCCIO DI CORI, M.D

BOSTON

Since electroencephalography gives reliable data concerning one type of cerebral activity, this technic has been employed as an aid in the study of alcoholism and the alcoholic psychoses. Loomis and associates,[1] in 1936, studied a patient during an alcoholic stupor and noted increase in the brain potentials and slowing of the rhythm. Gibbs and associates[2] reported that administration of alcohol first increases the voltage of fast frequencies but that later, as consciousness is lost, slow rhythms appear. Rosenbaum and associates[3] noted pathologic brain waves of the type seen in attacks of epilepsy in 4 patients with chronic alcoholism and convulsions.

An important electroencephalographic study of alcoholism was carried out by Davis and her co-workers.[4] In acute intoxication only slight changes occurred in the electroencephalogram, in spite of pronounced changes in mood, deportment and mental acuity; and clearly evident effects, namely, reduction in fast activity and a simultaneous increase in slow activity, occurred only when the level of awareness of the patient was greatly reduced. These authors also studied 15 nonpsychotic subjects who had been confined to a hospital for chronic alcoholism and reported that the "alcoholics appeared to be between the normals and the psychotics in respect to the normality and stability of their electroencephalographic records."

Clinical observations on patients with chronic alcoholism and alcoholic psychoses have led to certain interesting questions. For example, does prolonged excessive indulgence in alcohol lead to abnormalities in the electrical activity of the cortex? Are any electroencephalographic changes associated with the alcoholic psychoses? Does alcoholic deterioration or Korsakoff's psychosis result in a peculiar electroencephalographic pattern? Is there an epileptoid component in pathologic intoxication, and is the electroencephalogram an aid in detecting this? Finally, in patients with epilepsy associated with alcoholism ("rum fits") does the electroencephalogram show the dysrhythmias which have been described as characteristic of idiopathic epilepsy?

We have studied the electroencephalogram and clinical features of a series of patients with chronic alcoholism with and without psychosis and have paid special attention to epilepsy in association with chronic alcoholism; on the basis of this study we are able to give preliminary answers to some of these questions.

RECORDING AND CLASSIFICATION OF ELECTROENCEPHALOGRAMS

Electroencephalograms were recorded with a Grass six channel amplifying system. Electrodes were applied to both frontal, both parietal and both occipital area. Both monopolar and bipolar recordings were taken; for the former, interconnected leads from the mastoid served as an indifferent pole. Bipolar leads prove helpful in eliminating muscle artefacts in tense and restless patients. The tracings were obtained with the patient in a recumbent position, with the eyes closed, in a darkened and quiet room.

The records are classified as normal, borderline or abnormal on the basis of experience with hundreds of normal and abnormal subjects. A normal record is defined as one in which the brain wave rhythm has frequency of between 8 and 12 per second and in which the pattern is unchanged, or only slightly modified, by two minutes of hyperventilation. An abnormal record is defined as one in which the prevailing activity is outside the frequency range of 8 to 12 per second, or one which shows a decided change in the character of the pattern as a result of two minutes of overbreathing. Borderline records are those without a dominant frequency pattern or with characteristics of both normal and abnormal tracings. Certain subjective factors are of necessity involved in the classification of electroencephalograms, but in essence our classification of normal and abnormal records agrees with that of other investigators in the field.

1. Loomis, A.; Harvey, E. N., and Hobart, G.: Electrical Potentials of the Human Brain, J. Exper. Psychol. 19:239-249, 1936.

2. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: Effects on the Electroencephalogram of Certain Drugs Which Influence Nervous Activity, Arch. Int. Med. 60:154-166 (July) 1937.

3. Rosenbaum, M.; Murray, L.; Philip, P., and Goldman, D.: Convulsive Seizures in Delirium Tremens, Arch. Neurol. & Psychiat. 45:486-493 (March) 1941.

4. Davis, P. A.; Gibbs, F. A.; Davis, H.; Jetter, W. W., and Trowbridge, L. S.: The Effects of Alcohol upon the Electroencephalogram, Quart. J. Stud. on Alcohol 1:626-637 (March) 1941.

This hypothesis seems to·explain why so-called psychomotor electrical patterns (3 to 6 per second rhythmic slow waves) may be seen in patients who have no history of "psychomotor" clinical manifestations and yet may be associated with such attacks in other persons.

In the present study all patients with a history of episodes classified as of "psychomotor," "psychic equivalent or variant" or "amnesia" type also had focal, petit or grand mal seizures.

Evidence indicates that in a high voltage epileptic discharge high frequencies do not necessarily produce "overactivity" or slow frequencies "underactivity." This observation, as recorded here, applies only to the abnormal waves associated with epilepsy.

In the formation of the slow waves (random or rhythmic in the electroencephalograms of epileptic subjects) it is suggested that, although the periods of activity of the neurons are more or less synchronous (are simultaneous—show hypersynchrony), the resulting composite impulse discharges which presumably contribute to the slow potential changes are asynchronous and often of high frequency. In the case of fast waves (at least when rhythmic), on the other hand, the periods of activity of the neurons, as well as the impulse discharges, may be synchronous.

which nevertheless required in many instances an arbitrary diagnosis. Table 2 shows the diagnostic classification used, the numbers of patients in each category and the percentage of abnormal electroencephalograms obtained in each class. Also shown are the two control groups: 1. A group of 240 persons normally adjusted in the community who may serve as a base line, or norm, for all other diagnostic categories or subdivisions. Of this number, 10 per cent had abnormal electroencephalograms. 2. A group of 115 patients with essential or idiopathic epilepsy whose seizures began relatively late in life, at an average age of 35. This group should be compared with the group of patients with "rum fits," whose seizures also appeared relatively late in life, at an average age of 35. In table 2 the alcoholic disorders are arranged in order of rank, that is, in terms of the ascending incidence of abnormal electroencephalograms.

Chronic Alcoholism Without Psychosis.—It is interesting to note that in this group only 5 per cent of the electroencephalograms were abnormal. The tracings were taken when the period of acute intoxication responsible for the admission to the hospital was over and when the patient was clinically free of symptoms. Chronic alcoholism without psychosis, essentially the least complicated of the alcoholic disorders from the standpoint of formation of symptoms, is associated with the lowest percentage of electroencephalographic abnormality of any of the alcoholic syndromes. In fact, the percentage of abnormal electroencephalograms in this series was less than that encountered among control subjects normally adjusted in the community. Much has been written concerning the personality "defects" which are supposedly present in persons who readily establish the habit of dependence on alcohol. We have no electroencephalographic evidence that these patients exhibit abnormal cortical function. There is also no evidence that the duration of chronic alcoholism has any significant relation to the amount of electroencephalographic abnormality. Normal records were obtained from persons with a long history, as well as from those with a relatively short period, of heavy indulgence.

"Rum Fits."—Of the 24 patients with "rum fits," only 4 (17 per cent) had abnormal electroencephalograms, a surprising finding in view of the high percentage of abnormal records obtained for almost all other patients who had convulsions as an outstanding symptom. These patients will be discussed in more detail later.

Alcoholic Hallucinosis or Delirium Tremens.—A total of 34 patients had a condition diagnosed as alcoholic hallucinosis or delirium tremens, and a total of 7, or 21 per cent, had abnormal electroencephalograms. However, there a definite correlaton between the presence of active symptoms and electroencephalographic abnormality. Thirteen patients in the group were studied during active hallucinosis or delirium, and 6 of these, or 46 per cent, had abnormal electroencephalograms. On the other hand, 21 patients were studied after recovery from hallucinosis or delirium tremens, and only 1, or 5 per cent, had an abnormal record.

The data suggest that an abnormal electroencephalogram is related to active disease and that clinical recovery is associated with improvement in the pattern. An abnormal record is evidently not a prerequisite to the appearance of hallucinosis or delirium in a patient with chronic alcoholism. Although it seems likely, we have as yet no data to indicate that an abnormal electroencephalogram indicates greater susceptibility to hallucinosis or delirium tremens after heavy indulgence. However, an abnormal tracing obtained during the acute stage of disease is often indicative of a longer clinical course than is a normal one.

Undiagnosed Psychosis with Chronic Alcoholism.—In this group were placed 24 chronically alcoholic patients with psychosis of a relatively undifferentiated type not readily classified in other categories. Patients with many heterogeneous types of conditions were included here, but all were psychotic at the time of the electroencephalographic examination. Thirty-five per cent of the records were abnormal.

Pathologic Intoxication.—Patients in whom small amounts of alcohol produced disproportionately great outbursts of violent, aggressive overactivity with clouding of consciousness were regarded as exhibiting pathologic intoxication. Five patients in this category were studied after recovery from intoxication. Three had abnormal electroencephalograms. Both slow and rapid potentials were present in the abnormal tracings, but no tracing presented the paroxysmal dysrhythmia characteristic of the epileptic disorders.

Korsakoff's Psychosis.—Four patients whose illness was diagnosed as Korsakoff's psychosis were studied electroencephalographically during the period of notable impairment of mental functions; 1 of these was followed until recovery occurred under intensive treatment. Three of the 4 patients, including the patient whose condition later cleared up, had abnormal electroencephalograms. The fourth had a normal record despite a well marked Korsakoff psychosis. The patient who was followed during treatment showed improvement in the electro-

MATERIAL

A series of 157 patients with chronic alcoholism admitted to the Boston Psychopathic Hospital over a five year period, from 1939 to 1944, formed the basis of the investigation. In most instances only one electroencephalogram was taken for each patient, but for some of the patients repeated electroencephalograms were obtained, either during a single period of hospitalization or during successive admissions. The diagnostic classification of the type of alcoholic disorder from which the patient was suffering was decided after careful scrutiny of the hospital record. Special attention was given to the patients with epilepsy associated with alcoholism and to the clinical status of these patients on the day that the electroencephalogram was taken.

The electroencephalographic controls for these records of patients with chronic alcoholism consisted of tracings obtained from a series of 240 nurses, physicians, medical students and hospital personnel, between the ages of 18 and 40; 90 per cent of the control subjects were between 20 and 30 years of age. The percentage of abnormal electroencephalograms in this group was 10 per cent.

As an added control for the electroencephalograms of our patients with epilepsy associated with alcoholism ("rum fits") who had onset of seizures relatively late in life (at an average age of 35), the tracings were compared with the electroencephalograms of 115 patients with idiopathic epilepsy with an average age of onset of convulsions at 35. The records of the latter group were made available to us through Dr. and Mrs. F. A. Gibbs, from their collection of over 1,000 records of epileptic patients.

DATA AND RESULTS

In an analysis of the factors which may conceivably affect the incidence of abnormalities in the electroencephalogram in any heterogeneous group of patients, the age of the patients and the type of clinical disorder from which they suffer are of great significance.

In a recent study by one of us,[5] the effect of age and the clinical condition on the electroencephalographic abnormalities of a large group of neuropsychiatric patients was so striking that it has become imperative to analyze the electroencephalograms for all types of patients with these two factors in mind. We found that 24 per cent of our total group of 157 patients with alcoholic disorders had abnormal electroencephalograms. However, when the incidence of abnormalities was considered with relation to age (table 1), only 5 per cent of abnormal records was found in the age group from 20 to 30, whereas an incidence of 18 per cent was noted for the age group from 30 to 40, 19 per cent for the age group from 40 to 50 and 48 per cent for the age group of 50 and above. This trend of an increasing incidence of abnormalities in the older age

5. Greenblatt, M.: Age and Electroencephalographic Abnormality in Neuropsychiatric Patients, Am. J. Psychiat. **101**:82-90 (July) 1944.

groups is similar to that shown for the neuropsychiatric disorders in general and for several of the clinical diagnostic subgroups, for example, involutional melancholia, psychoneurosis and psychopathic personality.[2] In our control group, made up of nurses, physicians, medical students and hospital personnel, the majority were between 20 and 30 years of age, and the incidence

TABLE 1.—*Relation of Age to the Incidence of Electroencephalographic Abnormalities*

Patients with Chronic Alcoholism		
Age Group, Yr.	Number	Percentage with Electroencephalographic Abnormalities
20 to 30	21	5
30 to 40	58	18
40 to 50	52	19
50+	26	48
Control Subjects		
20 to 30	240	10

of abnormalities was 10 per cent. For the same age range, therefore, the alcoholic patients had an incidence of abnormal electroencephalograms of 5 per cent and the normal subjects an incidence of 10 per cent, a difference which is not significant (table 1).

The type of disorder from which the patient suffers is of major importance. Since, for the most part, there are no fundamental physiologic

TABLE 2.—*Relation of Clinical Classification of Alcoholic Psychoses to the Incidence of Abnormal Electroencephalograms*

Clinical Diagnosis	Number of Patients	Abnormal Electroencephalograms	
		Number	Percentage
Chronic alcoholism without psychosis	55	3	5
"Rum fits" (average age of onset, 35)	24	4	17
Alcoholic hallucinosis or delirium tremens	34	7	21
During active disease	(13)	(6)	(46)
After recovery (patient asymptomatic)	(21)	(1)	(5)
Undiagnosed psychosis with chronic alcoholism	24	8	35
Pathologic intoxication	5	3	..
Korsakoff's psychosis	4	3	..
Alcoholic deterioration	11	9	..
Total	157	37	24
Controls	240	24	10
Idiopathic epilepsy (average age of onset of seizures, 35)	115	86	75

or pathologic differences on which to base a classification of the alcoholic disorders, one is forced to resort to classification by clinical syndromes, which involves necessarily many subjective elements of interpretation. After careful consideration of the histories of the patients and the elimination of certain doubtful or unsatisfactory cases, we agreed on a workable scheme,

mental state improved. When the type of electroencephalogram for each patient was compared with the mental status of that patient, it appeared that the more clouded the mental picture at the time of the recording the more abnormal was the electroencephalogram (fig. 1).

Of 24 patients with "rum fits," only 4, or 17 per cent, had abnormal electroencephalograms; 3 of these 4 patients had clouding of consciousness, and the fourth was actively hallucinated at the time of the recording.

Idiopathic Epilepsy.—Because of the surprising observation that "rum fits" were associated with little electroencephalographic abnormality whereas almost all other conditions in which convulsions are an outstanding feature are associated with a high incidence of electroencephalographic abnormality, we decided to compare our observations on patients with "rum fits" with those on patients with idiopathic epilepsy. We were especially interested in controlling the age of onset of seizures because of the possibility that a low incidence of electroencephalographic abnormalities might appear in any group of patients with late onset of seizures. Accordingly, we obtained a group of 115 patients with idiopathic epilepsy with an average age of onset of seizures at 35, exactly comparable to the age of onset of seizures in the patients with "rum fits." The group of patients with idiopathic epilepsy was characterized by negligible alcoholic intake, no dependence of seizures on alcoholism and a high incidence of a family history of convulsions—all in direct contrast to the patients with "rum fits." The percentage of electroencephalographic abnormalities for the patients with idiopathic epilepsy was 75 per cent. A consideration of the relation of electroencephalographic abnormality to age of onset of epilepsy in patients with the idiopathic type showed that from youth to old age there was a decrease of 10 to 15 per cent in the incidence of electroencephalographic abnormalities. At comparable ages for onset of seizures, however, the incidence of abnormal electroencephalograms was strikingly higher for idiopathic epilepsy than for "rum fits."

COMMENT

Many investigations have established the fact that a high incidence of electroencephalographic abnormality is associated with the convulsive disorders and that the most significant feature is the paroxysmal dysrhythmia, so thoroughly studied by Gibbs and Lennox. The actual percentage of abnormal electroencephalograms varies with the individual series, but most workers agree that between 60 and 90 per cent of patients with

seizures have abnormal electroencephalograms. However, there is always the irreducible minimum who do not show abnormalities despite well substantiated convulsions. To a certain extent, this may be explained on the basis of the severity and frequency of the epileptic attacks —that is, patients with rare or infrequent seizures may show considerably less electroencephalographic abnormality than those with frequent or severe seizures. Age is another factor that may determine the amount of abnormality. There is evidence to indicate that the older the epileptic patients, the lower the percentage of electroencephalographic abnormality.[6]

The question arises whether persons without onset of seizures in childhood and without a family history of epilepsy (that is, without evidence of an inborn epileptic component), yet with seizures due to some other factor, have significant electroencephalographic abnormalities.[7] Only a few observations bearing on this question have been reported. A case of convulsions following abrupt withdrawal of barbiturates with a normal electroencephalogram has been reported.[8] We have observed several such cases of seizures following withdrawal of barbiturates in addicts who were not known to be epileptic and whose electroencephalograms were normal when the seizure was over. A similar example is that of a patient subjected to electric shock therapy. In such a patient electroencephalograms are usually normal before shock, and there is a rapid return to normal after the induced seizure subsides. Except in occasional patients subjected to numerous electrically induced fits in whom one sometimes sees prolonged alteration in the electroencephalogram, the ultimate pattern is normal and similar to the preshock pattern.

Our data lead us to believe that patients with "rum fits" have no inherited predisposition to epilepsy and have normal interseizure records despite years of heavy alcoholic indulgence and of seizures induced by alcohol. We believe that there is often confusion between cases of pure "rum fits" and cases of idiopathic epilepsy in which seizures may at times be precipitated by ingestion of alcohol. In the latter the onset of epilepsy usually precedes the alcoholism by some

6. Robinson, L. J.: Incidence of Abnormal Electroencephalograms in Epileptic Persons Over Forty Years of Age, Dis. Nerv. System **2**:55-58 (Feb.) 1941.

7. Lennox, W. G.: Alcohol and Epilepsy, Quart. J. Stud. on Alcohol **2**:1-11 (June) 1941.

8. Brownstein, S. R., and Pacella, B. L.: Convulsions Following Abrupt Withdrawal of Barbiturate: Clinical and Electroencephalographic Studies, Psychiatric Quart. **17**:112-122 (Jan.) 1943.

encephalographic pattern associated with clinical recovery.

Alcoholic Deterioration.—Eleven patients presenting the clinical picture of alcoholic deterioration were studied; 9 had abnormal electroencephalograms. However, the average age of these patients (49 years) was higher than that of the patients in the other diagnostic groups, and conceivably the electroencephalographic abnormality could in part be due to the factor of age.

Electroencephalographic Pattern and Prognosis of the Alcoholic Disorders.—The vast majority (80 per cent) of the patients with alcoholism were discharged from the hospital as improved within ten days. The remainder (20 per cent) were transferred to other mental disease institutions for more prolonged care and treatment because of the greater severity and chronicity of their illness. Fifty per cent of the patients who had abnormal electroencephalograms and only 11 per cent of the patients with normal electroencephalograms required more prolonged hospitalization. The abnormal electroencephalographic pattern was correlated not only with the presence of active hallucinosis, delirium and confusion but with a longer clinical course.

ALCOHOLISM AND EPILEPSY

When convulsions and chronic alcoholism appear together in the same patient, it is often a difficult problem to determine their precise etiologic relation. A history taken from the patient is often grossly unreliable because these patients have a tendency to obscure the relation between the two factors; for example, they date the convulsions before the onset of alcoholism or emphasize that seizures do not occur during the height of alcoholic indulgence but have their onset after the indulgence has ceased. When the latter claim is made, one must be suspicious of a primary withdrawal phenomenon, for sometimes there is a short lag between the cessation of drinking (often spontaneous, because of gastritis and vomiting) and the appearance of seizures.

A logical classification on the basis of the relation between convulsions and alcoholism would have to do justice to the many possible gradients of etiologic dependence of seizures on alcoholic indulgence. At one extreme, there would be patients who never had convulsions save at the height of alcoholism or shortly after abrupt withdrawal. Such a condition is already clinically well recognized and is given the name "rum fits," or "whisky fits." At the other extreme, there would be patients suffering from essential or idiopathic epilepsy with or without alcoholic indulgence, but with no manifest etiologic rela-

tion between the two. Between these two extremes there would be patients with a tendency to epilepsy in whom some indulgence in alcohol would at times be required to bring out the underlying predisposition.

We approach the problem by studying electroencephalographically and clinically the two extremes: (*a*) patients with "rum fits," with a clearcut etiologic relation between alcoholism and convulsions, and (*b*) patients with idiopathic epilepsy with insignificant indulgence in alcohol and with seizures temporally unrelated to alcoholic intake.

"Rum Fits."—Twenty-four patients, all males, were classified as having "rum fits." Their ages ranged from 26 to 52, with an average of 39. The duration of seizures ranged from days to years, with an average of four years. The duration of heavy alcoholism ranged from one-half year to twenty-seven years, with an average of fourteen years.

An average of ten years of heavy drinking occurred before the first admission to the hospital. Twenty-two of the patients had seizures
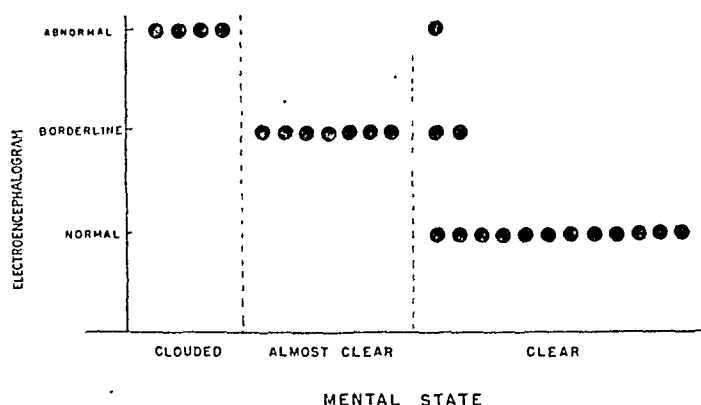
Relation between electroencephalographic classification and mental status of patients with "rum fits." Twenty-six electroencephalographic records were taken on 24 patients. The large circles represent one electroencephalogram each.

typical of grand mal attacks. The attacks of 1 patient were described as "fainting spells," and those of another consisted of clonic movements without loss of consciousness.

The histories of these patients were peculiar in that none had convulsions in youth or prior to the onset of heavy drinking. The earliest age of onset of seizures was 26 and the average age of onset 35. Not one of the patients had a family history of epileptic disorder.

The majority of patients with "rum fits" sought admission to the hospital because of postconvulsive clouding of consciousness, often accompanied by excitement. A few patients were followed during recovery from the clouded state, and it was evident that electroencephalographic abnormality disappeared as the clouded

THE HYPOTHALAMUS AND AFFECTIVE BEHAVIOR IN CATS

A STUDY OF THE EFFECTS OF EXPERIMENTAL LESIONS, WITH ANATOMIC CORRELATIONS

M. D. WHEATLEY, PH.D.

IOWA CITY

Evidence has accumulated which indicates that the hypothalamus may be concerned in certain elements of behavior the total pattern of which appears to be related to the outward manifestation of emotion. Stimulation of the hypothalamus in the region occupied by the medial bundle of the forebrain in the lateral part of the hypothalamus has been observed by Kabat and associates to cause mydriasis, increased respiration, struggling movements with clawing and biting, salivation, horripilation and sweating on the pads of the feet. In addition, cessation of peristalsis was noted, and sometimes evacuation of the bladder (Kabat, Anson, Magoun and Ranson [1]; Kabat, Magoun and Ranson [2]; Ranson, Kabat and Magoun [3]; Kabat,[4] and Kabat, Magoun and Ranson [5]). The points of stimulation were shown to be restricted largely to the lateral hypothalamic area. Similar results were obtained from anesthetized and unanesthetized cats. These reactions were not elicited when the infundibular stalk, the septum pellucidum, the anterior commissure, the thalamus and the internal capsule were stimulated with a current of the same intensity. The same general pattern of responses suggestive of rage had been observed by other investigators, but the precise area of stimulation had not previously been accurately localized (Karplus and Kreidl [6]). Dusser de Barenne and Sager [7] observed that when a small amount of strychnine was injected into the hypothalamus, cats displayed intense activity resembling sham rage; they hissed when approached and showed horripilation, mydriasis, salivation, defecation and urination. Strychninization of the thalamus caused hypersensitivity of the skin to temperature, touch and pain stimuli, but the cats did not show the affective responses observed on strychninization of the hypothalamus.

Somewhat similar results for electrical stimulation have been reported with human subjects. Grinker and Serota [8] stated that transsphenoidal stimulation by means of an electrode pushed into the nasal surface of the sphenoid bone about the middle of the floor of the sella turcica produced the usual general visceral effects: acceleration of the respiratory and the heart rate, dilatation of the pupils, elevation of blood pressure, increase in vasomotor tone, rise in body temperature, sweating and contraction of the bladder. Additional effects were reflected in the subjective and overt emotional reactions of the patients, e. g., profound anxiety and uncontrollable sobbing (Grinker and Serota [8]; Grinker [9]). All of the patients responded with

1. Kabat, H.; Anson, B. J.; Magoun, H. W., and Ranson, S. W.: Stimulation of the Hypothalamus with Special Reference to Its Effect on Gastrointestinal Motility, Am. J. Physiol. 112:214, 1935.

2. Kabat, H.; Magoun, H. W., and Ranson, S. W.: Electrical Stimulation of Points in the Forebrain and Midbrain, Arch. Neurol. & Psychiat. 34:931 (Nov.) 1935.

3. Ranson, S. W.; Kabat, H., and Magoun, H. W.: Autonomic Responses to Electrical Stimulation of the Hypothalamus, Preoptic Region and Septum, Arch. Neurol. & Psychiat. 33:467 (March) 1935.

4. Kabat, H.: Electrical Stimulation of Points in the Forebrain and Midbrain: The Resultant Alterations in Respiration, J. Comp. Neurol. 64:187, 1936.

5. Kabat, H.; Magoun, H. W., and Ranson, S. W.: Reaction of the Bladder to Stimulation of Points in the Forebrain and Midbrain, J. Comp. Neurol. 63:211, 1936.

6. Karplus, J. P., and Kreidl, A.: Gehirn und Sympathicus: I. Zwischenhirnbasis und Halssympathicus, Arch. f. d. ges. Physiol. 129:138, 1909; II. Ein Sympathicuszentrum im Zwischenhirn, ibid. 135:401, 1910; III. Sympathicusleitung im Gehirn und Halsmark, ibid. 143:109, 1911; IV., ibid. 171:192, 1918; VII., ibid. 215:667, 1927.

7. Dusser de Barenne, J. G., and Sager, O.: Ueber die sensiblen Funktionen des Thalamus opticus der Katze (Untersucht mit der Methode der örtlichen Strychninvergiftung; allegemeine Symptomatologie und funktionelle Lokalisation), Ztschr. f. d. ges. Neurol. u. Psychiat. 133:231, 1931.

8. Grinker, R. R., and Serota, H.: Studies on Corticohypothalamic Relations in the Cat and Man, J. Neurophysiol. 1:573, 1938.

9. Grinker, R. R.: Hypothalamic Functions in Psychosomatic Interrelations, Psychosom. Med. 1:19, 1939.

time; in addition, the seizures frequently occur in the absence of any known intake of alcohol. In a small series of such cases we found a high incidence of abnormal electroencephalograms comparable to that for idiopathic epilepsy without alcoholism.

In studying the brain waves of patients with convulsions, we found it important to know the exact mental status at the time of the electroencephalographic examination before evaluating the final normality or abnormality of the tracing because any residual confusion following a seizure may be associated with abnormalities which later clear up. This is particularly true of patients with "rum fits," for these patients are often hospitalized because of postconvulsive clouding, and the clouding of consciousness is frequently prolonged.

Not only postconvulsive confusion but active alcoholic hallucinosis is correlated with abnormal electrocortical activity, and often the hallucinosis is present long after the elimination of alcohol is completed. Surely, excessive alcoholism initiates a neurophysiologic change the persistency of which does not depend on a high level of alcohol in the blood.

An arrangement of clinical categories of chronic alcoholism on the basis of an increasing incidence of electroencephalographic abnormality (as in table 2) turns out to be a rough classification of these disorders according to the severity of the clinical picture, the chronicity of symptoms and, probably, the severity and extent of damage to the brain. The lowest incidence of electroencephalographic abnormality is found in cases of chronic alcoholism without psychosis, essentially the least complicated of all the alcoholic disorders from the standpoint of the formation of morbid symptoms. On the other hand, the highest incidence of electroencephalographic abnormality occurs in cases of alcoholic deterioration, an essentially fixed·psychosis with features of the organic reaction type. In our small series of patients with Korsakoff's psychosis (an outstanding paradigm of the "organic syndrome") there was a high incidence of electroencephalographic abnormality, and we anticipate eventual corroboration of this observation when a larger series of such patients has been collected. Relatively little abnormality is found for patients with delirium tremens or acute alcoholic hallucinosis, both disorders with rapid recovery. However, with chronic alcoholic hallucinosis the electroencephalogram tends to be more abnormal than with the acute type.

SUMMARY

In a study of the clinical histories and electroencephalograms of 157 patients with chronic alcoholism with and without psychosis, including patients with convulsions due to chronic alcoholism, the following observations were made:

The incidence of electroencephalographic abnormality in patients with chronic alcoholic disorders increases with age.

Persons with chronic alcoholism without psychosis, irrespective of the duration of drinking, show essentially nothing of significance in the electroencephalogram.

Chronic alcoholism with psychosis is in general associated with an incidence of electroencephalographic abnormality which is higher than normal. In patients with alcoholic psychosis the presence of confusion or hallucinations is frequently associated with electroencephalographic abnormality, and the disappearance of hallucinations or confusion is often accompanied by a change toward a more normal electroencephalogram.

No evidence of paroxysmal dysrhythmia was found in 5 patients with pathologic intoxication, although 3 of the 5 patients had abnormal electroencephalograms.

Of the patients with chronic alcoholism with psychosis, the highest incidence of electroencephalographic abnormality was found among those with deterioration or Korsakoff's syndrome. No specific electroencephalographic pattern was found in a group of 4 patients with Korsakoff's psychosis.

A relatively low incidence of electroencephalographic abnormality (17 per cent) was found in a series of 24 patients with "rum fits" (with a negative family history and a negative past history for epilepsy and with seizures occurring only in association with alcoholism). On the other hand, a relatively high incidence of electroencephalographic abnormality (75 per cent) was found in a large series of patients with idiopathic epilepsy with onset of seizures in the same age range as that of the patients with "rum fits."

In spite of the occurrence of seizures, patients with "rum fits" do not have the inborn epileptic predisposition observed in persons with idiopathic epilepsy.

An abnormal electroencephalogram may be of aid in predicting the duration of illness in patients hospitalized for chronic alcoholism.

Harvard Medical School.

rage is the caudal part of the hypothalamus. The phenomenon of "sham rage" has also been reported in man (Wortis and Maurer[21]).

Attempts to determine areas of the cortex specifically concerned in such a release phenomenon have not been consistently successful. Spiegel, Miller and Oppenheimer[25] reported that of 8 cats in which the frontal lobes were destroyed rostral to the sigmoid gyrus, only 1 showed definite rage reactions. Furthermore, Magoun and Ranson[26] removed the portions of the hemispheres rostral to the ansate sulcus in 8 cats, and none of the animals displayed the intense emotional hyperexcitability of sham rage, nor did these cats display any of the cataleptic symptoms that Barris[27] had reported to occur in cats after ablation of the same general area. Spiegel, Miller and Oppenheimer[25] observed that the production of lesions encroaching on the olfactory tubercle or in the fornices was followed by rage reactions. The most pronounced rage effects were observed in animals in which the lesions were said to affect the fornix, with involvement of the adjacent septum pellucidum. These authors also reported the appearance of rage reactions, and occasionally of cataleptic symptoms, following bilateral injury to the amygdaloid nuclei. No rage behavior followed elimination of the following regions: the sigmoid and coronal gyri; the lateral surface of the parietal lobe; the medial surface of the gyrus marginalis; the lateral surface of the temporal lobe, and the lateral, as well as the medial, surface of the occipital lobe.

Lesions of the hypothalamus itself in experimental animals have also been observed to be associated with changes in affective behavior. Bilateral lesions in the caudal part of the hypothalamus produce somnolence and catalepsy in cats, together with a decline in emotional reactivity (Ingram, Barris and Ranson[28]). Probably the most striking emotional changes were noted in wild monkeys, which became tame and showed no fear or anger after the placement of lesions dorsolateral to the mamillary nuclei (Ran-

son[29]). Kessler[30] found that unilateral destruction of the hypothalamus or of the ventromedial portion of the thalamus in cats resulted in positive rage reactions.

Ingram[31] frequently observed notable changes in "personality" in certain cats with bilateral hypothalamic lesions. These animals, formerly tame and friendly, became savage and would attack man with little hesitation. This picture was exactly the reverse of that noted in cataleptic animals. The lesions in these savage cats were usually in the medial portions of the hypothalamus.

The work to be reported in this paper was concerned with the following problems: (1) a study of changes in behavior in cats following production of lesions in various parts of the hypothalamus, with lesions in other regions of the brain as controls; (2) correlation of such changes in behavior as might be associated with the anatomic alterations caused by the destruction of nerve tissue, and, especially, an attempt to determine whether reactions of a savage type may follow destruction of any specific structural entities in the hypothalamus. In addition, various areas of other parts of the brain were destroyed or removed in 11 cats, not only to determine whether such lesions would ameliorate or intensify rage reactions in savage cats but to produce rage reactions in cats which had not become savage.

MATERIAL AND METHODS

In this experiment 42 cats were selected from several hundred on the basis of friendliness and failure to show aggressive behavior even when subjected to nociceptive stimuli. Only 1, a female cat, P36, showed the slightest tendency to become aggressive when roughed; otherwise, she was friendly and affectionate, and even when she showed such aggressiveness, she would respond immediately to friendly overtures with purring and other signs of feline friendliness and affection. The behavior of these animals was studied daily for several weeks before the placing of the hypothalamic lesions.

The cats were operated on while under anesthesia induced with pentobarbital sodium, and lesions were placed in the hypothalamus by use of the Horsley-Clarke stereotaxic instrument. Careful asepsis was maintained. Postoperative observations were made daily over periods ranging from several weeks to more than a year. Eleven of these cats were subsequently

24. Wortis, H., and Maurer, W. S.: "Sham Rage" in Man, Am. J. Psychiat. **98**:638, 1942.

25. Spiegel, E. A.; Miller, H. R., and Oppenheimer, M. J.: Forebrain and Rage Reactions, J. Neurophysiol. **3**:538, 1940.

26. Magoun, H. W., and Ranson, S. W.: The Behavior of Cats Following Bilateral Removal of the Rostral Portion of the Cerebral Hemispheres, J. Neurophysiol. **1**:39, 1938.

27. Barris, R. W.: Cataleptic Symptoms Following Bilateral Cortical Lesions in Cats, Am. J. Physiol. **119**:213, 1937.

28. Ingram, W. R.; Barris, R. W., and Ranson, S. W.: Catalepsy: An Experimental Study, Arch. Neurol. & Psychiat. **35**:1175 (June) 1936.

29. Ranson, S. W.: (*a*) Some Functions of the Hypothalamus, in Harvey Lectures, 1936, Baltimore, Williams & Wilkins Company, 1936, vol. 37, p. 92; (*b*) Somnolence Caused by Hypothalamic Lesions in the Monkey, Arch. Neurol. & Psychiat. **41**:1 (Jan.) 1939.

30. Kessler, M. M.: Spontaneous and Reflex Emotional Responses Differentiated by Lesions in the Diencephalon, Proc. Soc. Exper. Biol. & Med. **47**:225, 1941.

31. Ingram, W. R.: The Hypothalamus: A Review of the Experimental Data, Psychosom. Med. **1**:48, 1939.

expressions of fear, and, although none showed anger, stronger stimuli elicited tonic, and sometimes clonic, movements of the extremities comparable to the running and clawing movements reported for cats.

Mechanical stimulation of the floor of the third ventricle has also been reported as effective in producing outbursts of manic reactions in human subjects (Foerster and Gagel [10]). Singing, expressions of terror and rage, and general hyperactivity have been noted when this region was swabbed or disturbed during removal of pathologic growths with local anesthesia (Clark, Beattie, Riddoch and Dott [11]). However, White [12] found that in man mechanical and electrical stimulation of the hypothalamus produced bradycardia, a rise in blood pressure and a tendency to drowsiness or coma. He noted no alterations in respiration, nor could he detect any psychic or sensory changes.

Observations on emotional responses in man in clinicopathologic studies, while not as precise in the localization of the definite areas or nuclei concerned as is possible with animal experimentation, are nevertheless valuable in consideration of the possible anatomic correlates of emotional behavior. Practically all the disturbances consequent to lesions in and stimulation of the hypothalamus in experimental animals have been reported in man after trauma, operative manipulation, tumors, vascular lesions and infections of the hypothalamus. The behavior of the patients reflected a subjective phase, as well as the outward manifestations of emotion, some of them giving evidence of hallucinations, flight of ideas, terror, rage and anxiety. The behavior of others indicated pleasanter moods, which might be witty, jocular or obscene (Foerster and Gagel [10]; Cox [13]; Alpers [14]; Weisenburg [15];

Clark and associates [11]; Claude and Lhermitte [16]; Fulton and Bailey [17]; Cushing [18]).

Modern experiments attempting to delimit the various parts of the brain concerned with emotional expression through lesions and ablations were given their original impetus by Goltz [19] in 1892. He observed that a decorticate dog with injury to the corpora striata and the thalamus occasionally displayed emotional hyperexcitability suggestive of rage in response to innocuous stimuli. Similar results were obtained by other investigators with decorticate cats and dogs: Dusser de Barenne,[20] with decorticate cats, and Rothmann,[21] with a decorticate dog. Bard [22] and Bard and Rioch [23] made an exhaustive study of the effects of decortication on emotional expression in cats. They expressed the belief that the "sham rage" displayed by their experimental animals was due to the release of subcortical levels from cortical inhibition. The somatic component, or at least parts of the somatic component, of rage may possibly be elicited after all brain substance rostral to the mesencephalon is removed, but the full sham rage reaction requires that a portion of the posterior hypothalamus remain. This work indicates that the area most important for the full expression of

10. Foerster, O., and Gagel, O.: Ein Fall von Ependymcyste des III Ventrikels: Ein Beitrag zur Frage der Beziehungen psychischer Störungen zum Hirnstamm, Ztschr. f. d. ges. Neurol. u. Psychiat. **149**:312, 1933.

11. Clark, W. E. L.; Beattie, J.; Riddoch, G., and Dott, N. M.: The Hypothalamus: Morphological, Functional, Clinical and Surgical Aspects, Edinburgh, Oliver & Boyd, 1938, p. 212.

12. White, J. C.: Autonomic Discharge from Stimulation of the Hypothalamus, A. Research Nerv. & Ment. Dis., Proc. **20**:854, 1940.

13. Cox, L. B.: Tumours of the Base of the Brain: Their Relation to Pathological Sleep and Other Changes in the Conscious State, M. J. Australia **1**:742, 1937.

14. Alpers, B. J.: Relation of the Hypothalamus to Disorders of Personality, Arch. Neurol. & Psychiat. **38**:291 (Aug.) 1937.

15. Weisenburg, T. H.: Tumours of the Third Ventricle, with the Establishment of a Symptom-Complex, Brain **33**:236, 1910.

16. Claude, H., and Lhermitte, J.: Le syndrome infundibulaire dans un cas de tumeur du troisième ventricle, Presse méd. **25**:417, 1917.

17. Fulton, J. F., and Bailey, P.: Contribution to the Study of Tumors in the Region of the Third Ventricle: Their Diagnosis and Relation to Pathological Sleep, J. Nerv. & Ment. Dis. **69**:1, 145 and 261, 1929.

18. Cushing, H.: Papers Relating to the Pituitary Body, Hypothalamus and Parasympathetic Nervous System, Springfield, Ill., Charles C Thomas, Publisher, 1932.

19. Goltz, F.: Der Hund ohne Grosshirn, Arch. f. d. ges. Physiol. **51**:570, 1892.

20. Dusser de Barenne, J. G.: Récherches expérimentales sur les fonctions du systéme nerveux central, faites en particulier sur deux chats dont le néopallium avait été enlevé, Arch. néerl. de physiol. **4**:31, 1919.

21. Rothmann, H.: Zusammenfassender Bericht über den Rothmannschen grosshirnlosen Hund nach klinischer und anatomischer Untersuchung, Ztschr. f. d. ges. Neurol. u. Psychiat. **87**:247, 1923.

22. Bard, P.: (*a*) A Diencephalic Mechanism for the Expression of Rage with Special Reference to the Sympathetic Nervous System, Am. J. Physiol. **84**:490, 1928; (*b*) The Central Representation of the Sympathetic Nervous System as Indicated by Certain Physiological Findings, A. Research Nerv. & Ment. Dis., Proc. **11**:67, 1930; (*c*) On Emotional Expression After Decortication with Some Remarks on Certain Theoretical Views, Psychol. Rev. **41**:309 and 424, 1934; (*d*) Central Nervous Mechanisms for Emotional Behavior Patterns in Animals, A. Research Nerv. & Ment. Dis., Proc. **19**:190, 1939.

23. Bard, P., and Rioch, D. M.: A Study of Four Cats Deprived of Neocortex and Additional Portions of the Forebrain, Bull. Johns Hopkins Hosp. **60**:73, 1937.

tions, such as urination or defecation, displayed by a savage cat under similar circumstances, and (4) a mixture of poorly directed rage and general psychopathic manifestations, shown by a single animal, D187. This cat showed some motor defect, as indicated by ataxia and stiffness of gait. She had a sullen appearance, frequently panted and made useless movements.

The manner of development of the savage type of behavior varied. In general, a lack of favorable response to petting and fondling was one of the first changes noted. In some cats the complete pattern of savage behavior developed almost immediately or in a very short time after operation. In other cats several days to several weeks elapsed before all the physical manifestations of savageness were displayed. The amount and type of handling undoubtedly were important factors affecting this change, and every attempt was made to subject each of the 42 cats to the same treatment. Often, savage cats can be touched, or even pushed aside, just before they are fed and they are not so likely to attack at such times, especially if they see food. No other inducement produced this effect.

Records of weight were kept on these cats, more as a means of checking on their general health than of observing changes referable to obesity. Several cats which became savage showed proportionately greater increases in weight after the production of the lesions than did the animals which remained normal or those which showed varying degrees of change in behavior. Although the fat, protein and carbohydrate content of the food was not determined quantitatively, all the cats were fed equal portions of the same food. The principal difference in food intake was the rapidity of ingestion. The savage cats either ate hurriedly or wolfed their food, while normal cats given the same diet ate slowly, frequently taking several hours to consume their allowance. No attempt was made to keep measured records of the amount of activity before and after the placement of the lesion; therefore, comprehensive conclusions as to the mechanism producing this obesity are impossible (Hetherington and Ranson [32]; Tepperman, Brobeck and Long [33]). There exists the interesting possibility that the avid appetite observed in certain of the cats was part of a further behavioral change; thus, Brobeck, Tepperman

and Long [34] stated that the obesity in rats following hypothalamic lesions was due to "hypothalamic hyperphagia." It is certain that voracious, tigerish appetite and manner of eating were components of the behavior of many of the savage cats in my series, and 1 savage animal kept for many months on an unrestricted diet became exceedingly fat.

BEHAVIOR IN RESPONSE TO CONTROLLED STIMULI

Three general types of behavior were noted in the preoperative responses to electrical shock (recorded in vertical column B in tables 1 to 4): (1) responses in which the cat merely assumed a crouched position and a resigned attitude, with an occasional plaintive meow or light growl; (2) responses in which the cat attempted to escape or fought the harness or attacked some inanimate object in the cage, and (3) responses to the first shock by convulsive leaping and falling until exhaustion occurred. In these observations each cat was given at least fifty shocks with an interrupted faradic current from a Harvard inductorium. The current was of sufficient strength to cause a noticeable contraction of the shoulder muscles. In column B, tables 1 to 4, a response of the first type is indicated by 0. Escape reactions are indicated by *E*, and the number of attempts at escape during the course of the fifty stimulations is shown by the numeral following the corresponding *E*. Aggressive activity is indicated by *R*, and the number of such responses, by the numeral following the corresponding *R*. The convulsive type of reaction is indicated by *C*. When not responding with fear, rage or convulsions, the cat usually sat in a crouched position; sometimes it wandered around meowing or growling, but only definite attempts to escape or vicious attacks were counted during the experiment.

After recovery from the operation and after the treatment to minimize conditioning, as previously described, the cats were again subjected to this type of stimulation under conditions similar to those imposed before operation. The same three types of behavior patterns were observed; these are indicated in column A of the tables in the same manner as the reactions in column B. The principal difference noted between the preoperative and the postoperative reactions was the increased incidence of *escape and rage or attack reactions in most of* the cats which showed pronounced behavior changes or which became savage. In fact, nearly

32. Hetherington, A. W., and Ranson, S. W.: The Spontaneous Activity and Food Intake of Rats with Hypothalamic Lesions, Am. J. Physiol. **136:**609, 1942.

33. Tepperman, J.; Brobeck, J. R., and Long, C. N. H.: A Study of Experimental Hypothalamic Obesity in the Rat, Am. J. Physiol. **133:**488, 1941.

34. Brobeck, J. R.; Tepperman, J., and Long, C. N. H.: Experimental Hypothalamic Hyperphagia in the Albino Rat, Yale J. Biol. & Med. **15:**831, 1943.

subjected to the placing of various cortical lesions and ablations, and day by day records of their postoperative behavior were made.

An attempt was made by special means to arrive at a reasonably objective appraisal of the behavior of the animals when subjected to nociceptive stimuli. The animal to be studied was harnessed in such a way that two electrodes connected with a Harvard inductorium were in contact with the skin of the dorsal region. This harness did not interfere with freedom of movement. The cat was placed in a large cage arranged so that the observer was out of the animal's range of vision. The cage was equipped with noise makers and air blasts under remote control. Each cat was placed in the cage once prior to the operation and its behavior studied and recorded in terms of response to raucous noises, air blasts and shocks of faradic current of controlled intensity. After recovery from the operation, the animal was harnessed and placed in the cage repeatedly, but without being subjected to nociceptive stimuli. This was done to eliminate or minimize any conditioning effect. Later, responses to shocks and noises were noted, in an attempt to determine whether any changes in behavior response could be detected. This special method of study was a supplement to continual daily observation of the general attitudes and behavior of the cats in regard to contact with other animals and with human beings and in response to handling, feeding, and the like.

Motion picture records of the general behavior of the cats before and after operation were also made.

When the behavioral studies were concluded, the cats were killed, their heads perfused with a 10 per cent concentration of neutral solution of formaldehyde U. S. P. and the brains removed. After further fixation in the solution of formaldehyde, the diencephalic regions were dehydrated and embedded in pyroxylin.

Sections 50 microns thick were cut; every other section was stained with cresyl violet for cells, and the alternate sections, by the Weil method for myelin sheaths. In addition to the specimens from the 42 cats in the experimental series, there were available 28 brains from cats in which hypothalamic lesions had been placed for other purposes. Twenty-three of the animals in the latter group had become irritable or savage after operation. Five, however, had especially good behavior, despite the hypothalamic lesions, and were an important addition to the controls already available. Sections of their brains were also prepared. The 70 cat brains were studied microscopically, and attempts made to correlate behavioral changes with the location and extent of the injury to the brain.

Of the whole series, 16 specimens were from cats showing no postoperative change in behavior, in spite of the presence of hypothalamic lesions. These, and a group of animals subjected to "dummy" operations, constituted controls.

The operations for removal of cortical tissue were carried out by direct exposure and careful visualization of the areas to be excised. Careful asepsis was maintained; all bleeding was controlled, and the operations were performed with minimum trauma to areas not removed. During the postoperative period, fluids or food was forced as indicated by the condition of the animal.

GENERAL CHANGES IN BEHAVIOR

In this work only those outward manifestations which man has learned to associate with normal expressions of emotion in cats were studied. The subjective significance of these physical expressions can only be inferred. Bard [22d] has aptly expressed this viewpoint:

. . . It is doubtless impossible to determine whether a cat standing up to an attacking or threatening dog is subjectively experiencing rage or fear or a mixture of both, but on the supposition that different things should have different names it can be asserted that a normal cat is capable of displaying both rage and fear. When as a result of painful or rough treatment or in response to attack by another animal a cat reacts by spitting and aggressive biting and clawing, it is proper to call it one thing. When in response to similar stimuli or to other happenings, especially a sudden and unexpected loud noise, this same cat dashes off in a furtive manner, mewing plaintively, and tremblingly goes to cover on the first opportunity, it is necessary to designate this as something else. General usage leads one to call the former an expression of anger, the latter a display of fear or terror. It is significant that when observers of varied experience are shown these reactions by means of motion pictures in which the stimulus is not revealed they are unanimous in characterizing the one as a display of rage, the other as an exhibition of fear. This disposes of any possibility that knowledge of the stimulus plays an important part in determining the name given the behavior.

The behavior patterns of the cats in this experiment were not always so clearly cut. Some exhibited the same friendly behavior after operation as before. At the other extreme, some animals, when in the presence of the observer, continually showed all the physical manifestations which have been observed in normal cats when provoked to rage, i. e., mydriasis, horripilation, defecation, urination, vocalization of anger, spitting, lashing of the tail and a kyphotic attitude. They would attack the observer in a vicious, aggressive manner, biting and clawing, when attempts were made to pet them or when other innocuous stimuli were applied.

The exact degree of change in the intermediate types of behavior was often difficult to ascertain. In this account these postoperative reactions have been divided arbitrarily into four classes and are indicated as such in tables 2 to 4. These categories may be summarized as follows: (1) slight change, represented by animals usually harmless and friendly to a moderate degree, but with a tendency to use teeth or claws in escaping painful stimuli; (2) variable behavior, represented by cats which responded favorably to petting but often became savage when roughed, at such times showing many of the physical manifestations of rage; (3) definite and pronounced change, shown by cats which would not respond favorably to petting and displayed signs of rage when approached by the observer, but failed to present one or more of the physical manifesta-

all the animals tested in the latter group responded violently to each shock. There were some exceptions. In several animals preoperative escape responses were transformed to rage responses after operation.

It was not possible to discern a good correlation between the intensity of the stimulus (as measured by separation of the primary and the secondary coil) and the type of response from one animal to another. Some cats responded to light stimuli. With others it was necessary to increase the intensity of current until the

from a quantitative standpoint, it is obvious that the animals which manifested definite changes in affective behavior responded to the shocks in a characteristically more violent fashion.

Responses to raucous, frightening noises were less constant, both before and after operation. While the noises caused a relatively large number of fear reactions, changes in response consistent with altered type of behavior were not general. This phase of the work may be dismissed with the comment that animals of all types were usually capable of showing true fear
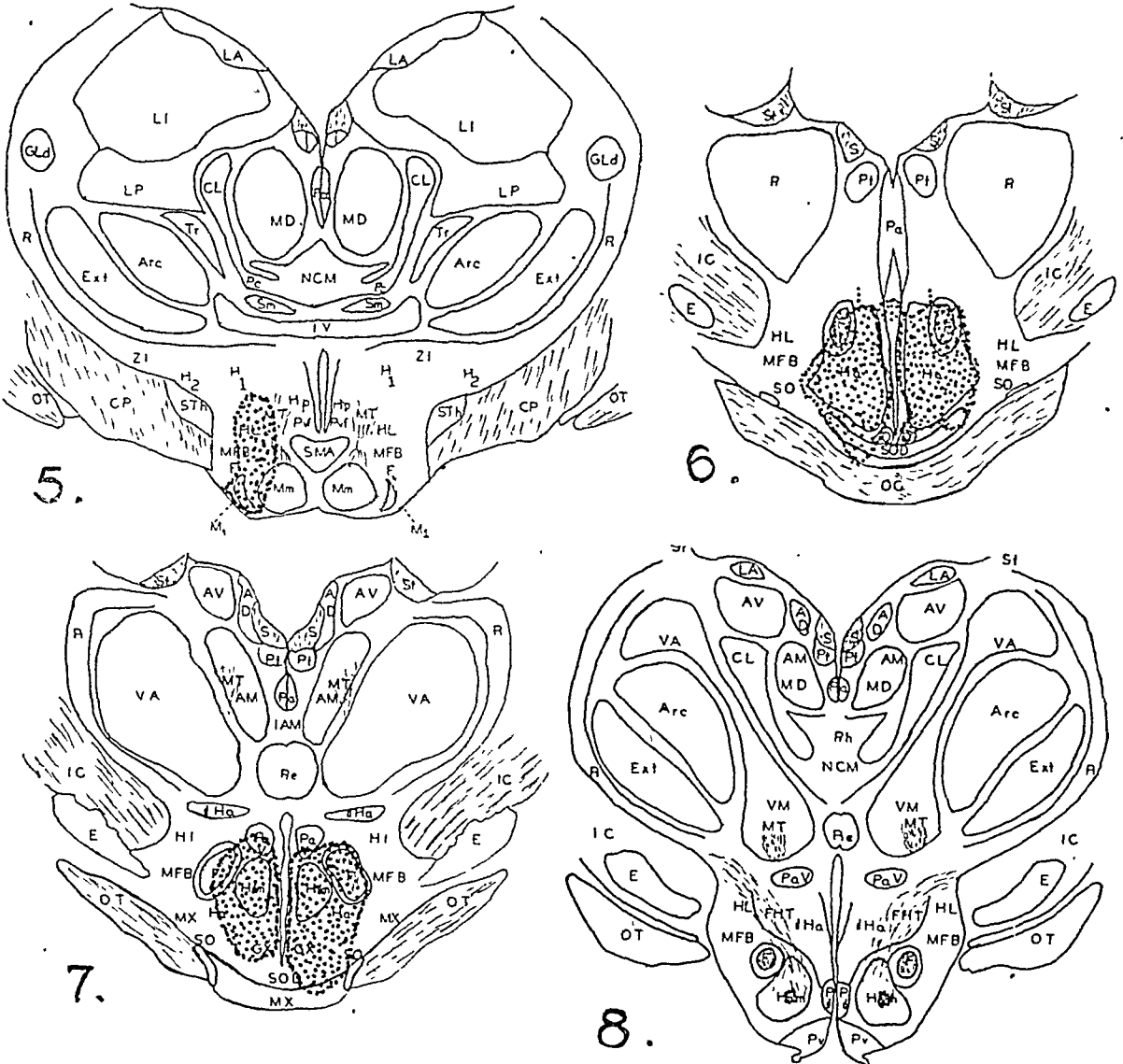
Figs. 5-8.—Figure 5 (cat P16), right unilateral lesion in the mamillary region; 6 (cat P6), bilateral lesions in the anterior hypothalamic areas; 7 (cat P6), bilateral lesions in the dorsal hypothalamic nuclei, and 8 (cat P6), spots of gliosis in the extreme anterior tip of the ventromedial hypothalamic nuclei.

shoulder muscles contracted. Furthermore, there was no really satisfactory correlation between the preoperative and the postoperative stimulus thresholds. In general, the intensity was the same, but when changes were necessary, this change could not always be correlated with the type of behavior pattern which developed after operation. However, although these attempted objective tests were not altogether satisfactory

behavior in response to noise, but that this type of stimulation was frequently ignored entirely, both before and after operation.

ANATOMIC OBSERVATIONS AND
ILLUSTRATIVE PROTOCOLS

Because of the importance of a precise analysis of the destruction caused by the experimental lesions, the nuclear configuration correlated with
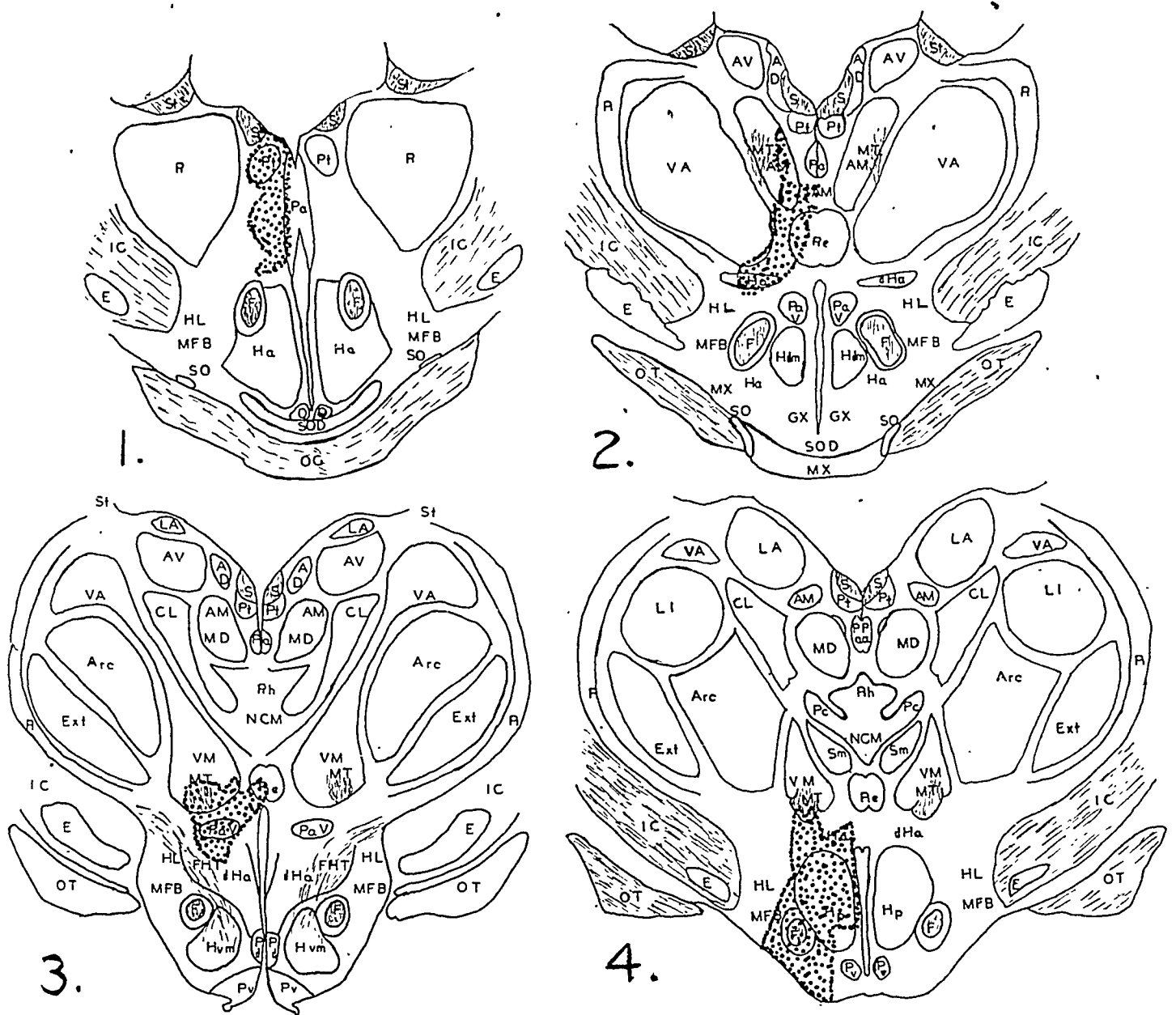
Figs. 1-4.—Lesions in the brain of cats showing normal postoperative behavior. *1* (cat P16), right unilateral thalamic lesion above the anterior hypothalamic area; *2* (cat P16), right unilateral thalamic lesion above the dorsomedial hypothalamic nucleus; *3* (cat P16), right unilateral lesion above the ventromedial hypothalamic nucleus; *4* (cat P16), right unilateral lesion in the posterior hypothalamic nucleus.

In these figures and in figures 9 to 21, the diencephalic structures are designated as follows: *AD*, nucleus anterodorsalis; *AM*, nucleus anteromedialis; *Arc*, nucleus ventralis pars arcuata; *AV*, nucleus anteroventralis; *CL*, nucleus centralis lateralis; *CP*, cerebral peduncle; *dHa*, dorsal hypothalamic area; *E*, nucleus entopeduncularis; *Ext*, nucleus ventralis pars externa; *F*, fornix and nucleus perifornicalis; *FHT*, pallidohypothalamic fibers; *GLD*, nucleus geniculatus lateralis dorsalis; *GX*, Ganser's commissure; H_1, H_1 field of Forel; H_2, H_2 field of Forel; *Ha*, anterior hypothalamic area; *Hdm*, nucleus hypothalamicus dorsomedialis; *HL*, nucleus hypothalamicus lateralis; *HP*, tractus habenulopeduncularis; *Hp*, nucleus hypothalamicus posterior; *Hvm*, nucleus hypothalamicus ventromedialis; *IAM*, nucleus commissuralis interanteromedialis; *IC*, internal capsule; *IV*, nucleus commissuralis interventralis; *LA*, nucleus lateralis pars anterior; *LI*, nucleus lateralis pars intermedia; *MD*, nucleus medialis dorsalis; *MFB*, medial forebrain bundle; *Ml*, nucleus mamillaris lateralis; *Mm*, nucleus mamillaris medialis; *MT*, mammillothalamic tract; *MX*, Meynert's commissure; *NCM*, nucleus centralis medialis; *O*, nucleus suprachiasmaticus; *OC*, optic chiasm; *OT*, optic tract; *Pa*, nucleus paraventricularis anterior; *PaV*, nucleus hypothalamicus paraventricularis; *Pc*, nucleus paracentralis; *Pd*, nucleus hypothalamicus periventricularis dorsalis; *Pt*, nucleus parataenialis; *Pv*, nucleus periventricularis arcuatus; *Pvf*, periventricular fibers; *R*, nucleus reticularis; *Re*, nucleus reuniens; *Rh*, nucleus rhomboidalis; *S*, stria medullaris; *Sm*, nucleus submedius; *SMA*, nucleus interstitialis supramamillaris; *SO*, nucleus supraopticus; *SOD*, nucleus supraopticus diffusus; *St*, stria terminalis; *STh*, nucleus subthalamicus; *Tr*, transition area; *VA*, nucleus ventralis pars anterior; *VM*, nucleus ventralis pars medialis, and *ZI*, zona incerta.

nucleus supraopticus diffusus and the nucleus hypothalamicus dorsomedialis. Cat P16, which also showed no postoperative change in behavior, had a unilateral lesion on the right side extending from the stria medullaris down in a slanting direction through the hypothalamus to the right nucleus mamillaris lateralis. The following protocol is typical for the cats which showed no change in behavior. The results of electrical stimulation are indicated in columns A and B of table 1.

time making friendly advances to the observer. She was fond of her food but ate daintily. Her fur was spotless and well groomed. When in estrus she showed the usual female attitude toward male cats.

On April 28, she was operated on while under anesthesia induced with pentobarbital sodium, and bilateral lesions were placed in the hypothalamus with a direct current of 3 milliamperes. The time of electrolysis was thirty to sixty seconds. She was kept in a warm chamber (31 C.) during the period of recovery.

The period of convalescence was brief, and by May 3, she was eating all food. She showed no change from her normal preoperative behavior except during the first few days, when she was not lively enough to play.
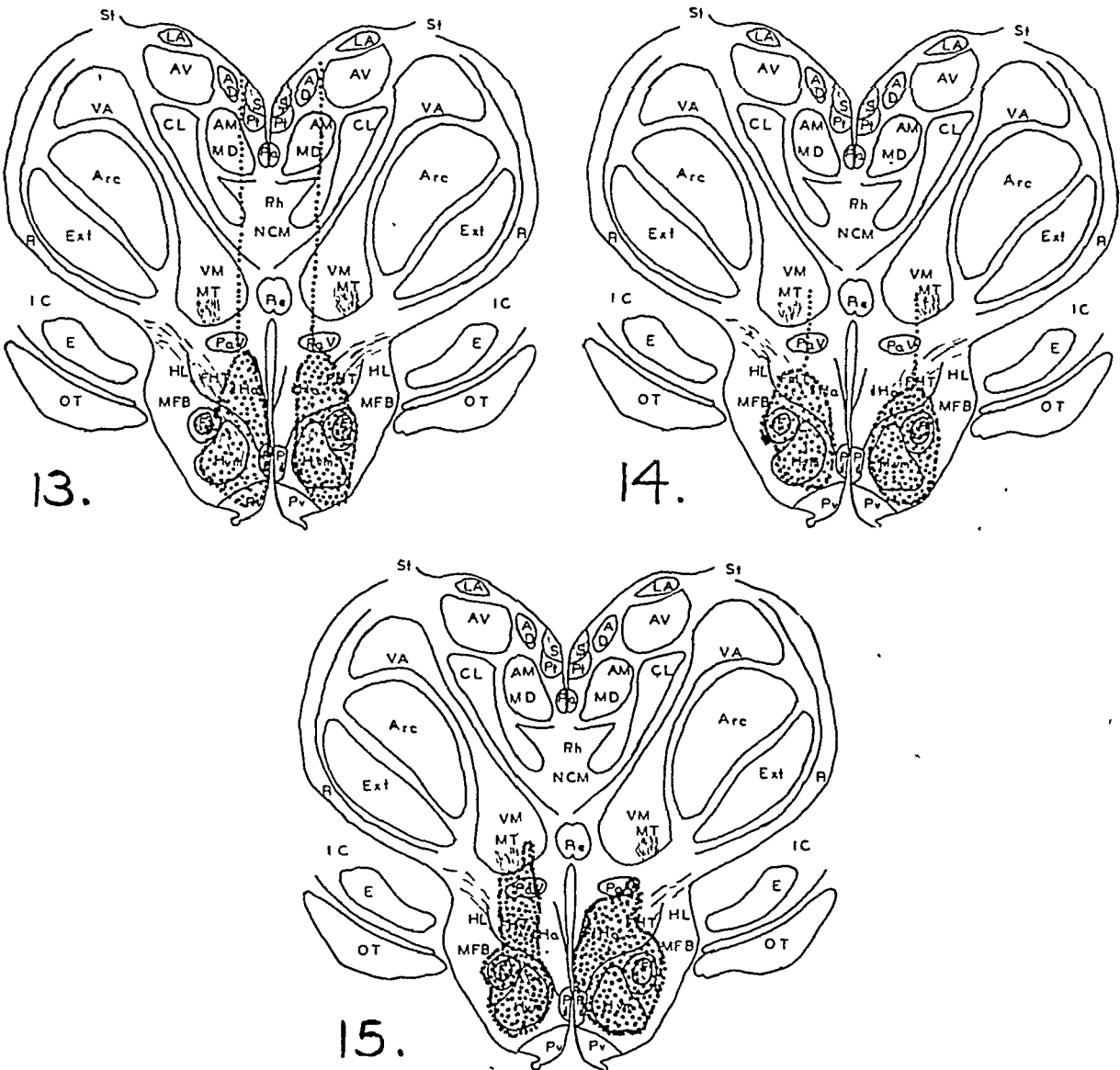
Figs. 13-15.—Figure *13* (cat P20), bilateral lesions in the ventromedial hypothalamic nuclei; *14* (cat P29), bilateral lesions in the ventromedial hypothalamic nuclei, and *15* (cat P31), bilateral lesions in the ventromedial hypothalamic nuclei.

CAT P16.—This cat, a small but sexually mature female, was very friendly to people and to all other cats. When she was handled roughly, she did not use her claws or teeth in attempting to escape. She responded immediately to petting with such signs of feline pleasure as rubbing against the observer, purring and other vocalizations. She was exceedingly playful and when out of her cage would gambol with other cats or play with inanimate objects. She spent much

Even when sick she responded favorably to petting and did not become irritable when roughed. As shown in table 1, the incidence of rage responses when she was subjected to electric shock was not increased. The lesions are illustrated in figures 1, 2, 3, 4 and 5 and are summarized in table 1.

Table 2 summarizes the structures damaged or destroyed in the cats which showed slight

stereotaxic measurements as worked out by Ingram, Hannett and Ranson [35] was followed. The terminology used conforms with that adopted by the Association for Research in Nervous and Mental Disease (Rioch, Wislocki and O'Leary [36]).

The nuclei and well established tracts most frequently involved by the lesions are indicated in tables 1 to 4. Slight damage to one of these structures is indicated by *S*. *X* denotes complete destruction. The amount of damage between these two extremes was estimated in relation to the gross size of the remaining parts. *E* denotes a range of destruction from slight damage to loss of one-half the structure, and *M* indicates loss of more than one-half but less than complete destruction. These symbols used alone denote bilateral and symmetric involvement. Unilateral damage is indicated by *L* or *D* before the *S, E, M* or *X*; *L* means that the damage was restricted to the left side; *D*, to the right side.

The cats subjected to blank operations as controls showed no postoperative changes in be-

Figs. 9-12.—Lesions in the brain of cats showing savage postoperative behavior. *9* (cat P42), lesions above the optic chiasm; *10* (cat P42), lesions in the region of the dorsomedial hypothalamic nuclei; *11* (cat P42), lesions in the region of the ventromedial hypothalamic nuclei; *12* (cat P42), lesions in the posterior hypothalamic area.

plete destruction. The amount of damage between these two extremes was estimated in relation to the gross size of the remaining parts. *E* denotes a range of destruction from slight

35. Ingram, W. R.; Hannett, F. I., and Ranson, S. W.: The Topography of Nuclei of the Diencephalon of the Cat, J. Comp. Neurol. 55:333, 1932.

36. Rioch, D. M.; Wislocki, G. B., and O'Leary, J. L.: A Précis of Preoptic, Hypothalamic and Hypophysial Terminology, with Atlas, A. Research Nerv. & Ment. Dis., Proc. 20:30, 1940.

havior, and observations on them are not included in the tables. Sixteen cats remained friendly and displayed normal behavior despite the variety of destructive lesions indicated in table 1. The lesions in certain typical members of this group are illustrated in figures 1 to 8. Cat P6 (figs. 6, 7 and 8) showed no definite change in behavior despite destruction of the anterior hypothalamic area, Ganser's commissure, the suprachiasmatic nucleus and the supraoptic nucleus, with severe damage to the fornix, the perifornical area, the

Figs. 16-21.—Lesions in the brains of cats showing slight change in postoperative behavior. *16* (cat P1), bilateral lesions in the ventromedial region of the thalamus and the dorsomedial area of the hypothalamus above the ventromedial hypothalamic nuclei; *17* (cat P1), bilateral lesions destroying the ventromedial thalamic structure and the dorsomedial hypothalamic structures in the posterior hypothalamic areas; *18* (cat P15), bilateral unilateral lesion in the region of the left dorsomedial hypothalamic nucleus; *19* (cat P15), unilateral lesion in the region of the left ventromedial hypothalamic nucleus; *20* (cat P37), unilateral damage to the right ventromedial hypothalamic nucleus, and *21* (cat P37), lesions in the posterior hypothalamic areas.

TABLE 1.—*Data on Sixteen Cats with Hypothalamic Lesions Displaying Normal Behavior*

Cat	Behavior	Shock Response B	A	Hvm	Hdm	Hp	Ha	dHa	Sod	So	O	Ml	Mm	Pav	Pd	Pv	Hl	Pvf	Sm	Re	Rh	Vm	Ncm	Fht	F	Gx	Mx	Mt
P 6	Normal	R10	R8	E	M		X	M	M	X	X				S		S	S	E			S				M	X	E	X
P11	Normal	0	0		S	E											S		E		S								X
P11	Normal	0	0																										
P16	Normal	R8	R4			D M	S	D E		L M		D X	D S	D X		D X	S	D M	D E		D M				D E	D X			D E
P17	Normal	E13	R3					S										E							E				
P19	Normal	E1	0				S																						
P26	Normal	0	0	L E			S		E	L M	X						L S								L X	M	X	X	L X
P32	Normal	0	0																										
P33	Normal	R1	0		M		E	E									M	M	E			S	E		X	X	X	M	
P39	Normal	0	0			M			X	X	X	X	S		E X	E		E							X	X	X	M	X
P14	Normal			L M			S	S	E	X	X			M		X		S	E		S		S					M	X
DI7	Normal			L S			E		E	X						S			E		S		S					X	
DI11	Normal																												
DI57	Normal				M																								
DI100	Normal																												
DI165	Normal																												

* In this table, and in the accompanying tables, 0 indicates absence of aggressive response; R, aggressive response, and C, convulsive response. A numeral following a letter indicates the number of times such a response was elicited.

† In this table, and in the accompanying tables, S indicates slight damage; X, complete destruction; E, slight damage to destruction of one-half the structure, and M, destruction of more than one-half the structure. D, placed before one of these letters, indicates that the lesion was limited to the right side, and L, that it was restricted to the left side. Hvm indicates nucleus hypothalamicus ventromedialis; Hdm, nucleus hypothalamicus dorsomedialis; Hp, nucleus hypothalamicus habenulopeduncularis; Ha, anterior hypothalamic area; dHa, dorsal hypothalamic area; Sod, nucleus supraopticus diffusus; So, nucleus supraopticus; O, nucleus suprachiasmaticus; Ml, nucleus mamillaris lateralis; Mm, nucleus mamillaris medialis; Pav, nucleus hypothalamicus periventricularis; Pd, nucleus hypothalamicus periventricularis dorsalis; Pv, nucleus periventricularis arcuatus; Pvf, nucleus hypothalamicus lateralis; Sm, nucleus submedius; Re, nucleus reuniens; Rh, nucleus rhomboidalis; Vm, nucleus ventralis pars medialis; Ncm, nucleus centralis medialis; Fht, nucleus periformicalis; F, fornix and nucleus perifornicalis; Gx, Ganser's commissure; Mx, Meynert's commissure, and Mt, mamillothalamic tract.

‡ Section of stalk resulting in degeneration of supraoptic nucleus.

TABLE 2.—*Data on Sixteen Cats with Hypothalamic Lesions Displaying a Slight or Variable Change in Behavior*

Cat	Behavior Change	Shock Response B	A	Hvm	Hdm	Hp	Ha	dHa	Sod	So	O	Ml	Mm	Pav	Pd	Pv	Hl	Pvf	Sm	Re	Rh	Vm	Ncm	Fht	F	Gx	Mx	Mt
P 1	Slight	R12	R10	E	X	M		M						X				S	E	X	X	X	X		M	M			X
P 7	Slight	E 4	E20	S	X		E	M		S				S					E						E	S	X		
P 8	Slight	R15	R20				M	S	E	S				E			S		E		S				E	X	S		
P15	Slight	R 3	R 6	L M	L E	L E		L S	L E			L M		L M			L M	L S			L E		L E		L X	L X	L X		L X
P27	Slight	0	R 3			D E		L E				D X	L E	D E			D M	D E		L E		L E	D S		D X	D X			D E
P37	Slight	0	0	D M		D E		D E		E			D E		S			D E							S				
P38	Slight	C	C	S	M		E	E	E	X	M		M		S				M			E			X	M	M		X
P43	Slight	0	R50			X	M		X	X	X	X					M		E			E				X	E		
P10	Variable	R1t	R50	M	E			S	M	E			E	E		E		S		S			M	E		S	S	M	M	
P28	Variable	E 1	R20	S		E	M	E	X				E	E	S		S		M		M				M	M			X
P36	Variable	R 6	R22			L E	L E	L E		X				S			L E			L S			L M	L S		L S	L S			L X
P40	Variable	R16	R24			E	E	E	M	X		L X				DM	E								DM	L X			
DI31	Variable			M	M		M	E	M	X	X		E												M	M			
DI73	Variable			E	X	S	E	E	F	X	X		E		X										M	E	M		
DI86	Variable			X	M	E	E	E	M	X	X		E	E	M	S						E			E	E	M		
DI136	Variable			M	M		E		M	E	E				E									M	M	E		E	

TABLE 3.—*Data on Seventeen Cats with Hypothalamic Lesions Displaying Decided Change in Behavior*

Cat	Behavior Change	Shock Response B	A	Hvm	Hdm	Hp	Ha	dHa	Sod	So	O	Ml	Mm	Pav	Pd	Pv	Hl	Pvf	Sm	Re	Rh	Vm	Nem	Fht	F	Gx	Mx	Mt
																												Nuclei and Tracts Damaged or Destroyed
P 5	Decided	0	0	X	X	:	M	S	E	:	:	:	:	:	M	E	:	E	:	:	:	:	:	X	X	X	E	:
P12	Decided	E 4	R.40	X	X	M	E	E	:	:	:	:	:	E	M	E	E	E	:	:	:	:	:	X	M	:	:	S
P18	Decided	R 2	R.50	X	M	S	E	S	E	:	:	:	:	E	:	:	S	S	:	:	:	:	:	X	X	:	:	:
P23	Decided	O	O	M	S	:	S	:	S	:	:	:	:	:	:	X	:	:	:	:	:	:	:	:	:	M	:	:
P25	Decided	R 6	C	X	S	:	E	E	:	:	:	LX	S	E	:	:	S	S	S	:	:	:	:	E	:	M	:	E
P35	Decided	0	:	M	M	M	M	M	:	:	:	:	S	E	:	:	E	:	:	:	:	:	M	M	:	S	:
P41	Decided	R 1	R 1	E	E	E	E	:	X	:	:	:	:	:	E	E	E	:	:	:	:	M	M	:	E	M	E	E
DI 8	Decided	:	:	X	S	E	S	S	X	:	:	:	:	X	S	S	E	E	:	:	:	X	M	E	S	X	:	:
DI20	Decided	:	:	X	M	M	E	E	X	X	:	:	M	X	X	X	X	X	M	:	:	X	X	E	X	X	M	M
DI42	Decided	:	:	M	X	X	X	X	X	X	E	:	S	X	X	X	M	E	M	:	:	X	M	E	M	S	:	E
DI66	Decided	:	:	X	E	M	M	M	X	E	X	:	E	M	X	X	E	E	M	:	:	X	M	E	E	E	:	E
DI72	Decided	:	:	X	X	E	E	E	X	X	X	:	E	E	X	X	E	M	E	:	:	M	E	X	X	E	E	E
DI102	Decided	:	:	M	M	M	E	:	E	E	:	:	:	E	M	M	M	M	:	:	E	X	X	:	X	M	E	:
DI142	Decided	:	:	X	X	M	E	S	M	S	:	:	:	E	X	X	:	E	S	:	E	X	X	X	X	E	E	E
DI115	Decided	:	:	X	E	E	M	:	E	E	:	:	E	:	X	X	:	E	:	:	:	X	X	X	X	E	E	:
DI113	Decided	:	:	X	E	M	M	E	M	E	:	:	:	E	X	X	:	E	:	:	:	X	X	X	X	M	M	:
DI158	Decided	:	:	X	X	S	M	S	M	X	:	:	:	X	X	M	:	M	:	:	:	X	E	X	X	X	X	:

TABLE 4.—*Data on Nineteen Cats with Hypothalamic Lesions Displaying Savage Behavior*

Cat	Behavior	Shock Response B	A	Hvm	Hdm	Hp	Ha	dHa	Sod	So	O	Ml	Mm	Pav	Pd	Pv	Hl	Pvf	Sm	Re	Rh	Vm	Nem	Fht	F	Gx	Mx	Mt
																												Nuclei and Tracts Damaged or Destroyed
P 2	Savage	E 5	R.50	X	X	E	E	E	E	LX	:	:	:	S	M	X	S	E	:	:	:	:	:	X	X	X	E	:
P 9	Savage	0	R.50	X	M	X	E	E	M	X	E	:	:	:	X	X	E	E	:	:	:	:	:	X	X	X	X	:
P20	Savage	R 1	R.50	X	E	S	:	E	:	:	X	:	:	S	:	X	S	E	:	S	:	:	:	X	X	:	:	:
P22	Savage	R 1	R.50	X	X	S	M	E	E	X	:	:	:	E	:	X	S	E	:	:	:	:	:	X	X	X	X	:
P24	Savage	O	O	X	M	S	S	M	M	:	:	:	:	:	X	X	S	M	E	:	:	:	:	X	E	M	M	M
P29	Savage	R 5	R.50	X	S	S	LE	E	S	:	:	:	:	M	M	M	E	E	:	M	:	:	:	X	X	M	:	E
P30	Savage	C	:	X	LM	M	S	M	S	:	:	:	:	E	M	:	S	E	:	S	:	:	:	X	X	E	E	DM
P31	Savage	:	:	X	E	S	E	E	E	:	:	:	:	X	M	:	E	S	:	:	E	E	S	X	X	X	:	:
P34	Savage	R 1	R.50	X	M	M	S	M	E	:	:	:	M	E	:	:	E	S	:	:	E	:	:	X	X	E	E	:
P42	Savage	R 1	0	M	E	E	M	X	E	X	:	:	E	X	M	:	M	M	:	:	M	:	:	X	X	X	X	M
DI1	Savage	:	:	X	X	:	E	S	E	E	S	:	:	M	:	S	:	E	:	S	:	:	:	X	X	X	X	E
DI30	Savage	:	:	X	E	E	E	M	E	X	X	:	M	M	M	:	M	M	:	:	:	:	:	X	E	X	X	X
DI61	Savage	:	:	X	X	:	S	X	E	:	X	:	E	X	X	:	E	E	:	M	:	E	:	X	X	X	E	E
DI135	Savage	:	:	X	E	E	E	X	E	:	E	:	:	X	M	:	E	E	:	S	:	:	:	X	X	M	:	:
DI111	Savage	:	:	X	M	:	M	M	M	:	:	:	S	M	:	:	S	E	:	:	:	:	:	X	X	M	M	:
DI151	Savage	:	:	X	S	E	E	E	E	:	:	:	:	S	:	:	E	E	:	:	:	:	:	X	X	:	:	:
DI155	Savage	:	:	X	S	S	E	E	E	:	:	:	:	:	:	:	S	E	:	:	:	:	:	X	X	X	X	:
DI167	Savage	:	:	X	X	S	M	E	X	X	X	:	:	X	X	:	M	E	:	:	:	:	:	X	X	X	:	:
DI87	Psychopathic	:	:	X	X	X	M	M	M	X	X	DX	M	E	X	:	M	X	:	:	:	:	:	X	X	X	X	DX

308

postoperative changes in behavior and in those in which the behavior pattern was designated as variable. In these cats, as in the animals showing no change, a wide variety of hypothalamic structures was destroyed or damaged to some degree; yet no single structure was consistently injured or eliminated. It is perhaps significant, however, that the incidence of involvement of the regions of the ventromedial and dorsomedial nuclei was increased in these groups, as compared with the cats in the first group. It is also noteworthy that despite bilateral destruction of the ventromedial area of the dorsal thalamus in certain animals, these cats' did not become truly savage. Cat P1 (figs. 16 and 17) is an example. This animal had an increased tendency to growl. When disturbed, he would use his claws in attempting to escape rough treatment but always responded favorably to petting and never displayed a vicious attitude. Interesting information on the relative absence of effect of a unilateral lesion is given by cat P15 (figs. 18 and 19) and cat P37 (figs. 20 and 21), which had extensive unilateral damage but did not become savage and might easily be classed as friendly. Cat P43 (table 2) is an interesting example of the effects of a lesion in the caudal part of the hypothalamus. This cat was somnolent for a week after the operation; yet he became irritated when roughed, growling and using his claws and teeth. He was not aggressive, however, and would respond immediately to petting with all the signs of pleasure of a friendly cat.

In tables 3 and 4 are tabulated the nuclei and tracts destroyed or damaged in the cats which became savage or showed pronounced change in the direction of savageness. Not one of these cats showed any postoperative tendency to respond favorably to petting. Their attitude and behavior have already been described, and this description holds for the group, with allowance for some individual differences with respect to certain items.

As the tables show, there was an extensive sampling of hypothalamic structures involved by lesions in these cats. It is important to point out that there was relatively little involvement of the dorsal thalamus, especially in the extremely savage cats. Also, while the lateral hypothalamic area was frequently encroached on, it was usually only slightly damaged, and in some cats it remained quite intact. The striking thing was the almost universal incidence of injury to the medial hypothalamic nuclei in these animals. In not all, however, was the degree of damage uniform. The most consistent results as to both incidence and degree were noted in the nucleus

hypothalamicus ventromedialis. Most of the cats exhibiting a pronounced change in behavior had the ventromedial hypothalamic nucleus destroyed. All the savage cats showed complete destruction of this nucleus except cat P42 (figs. 9, 10, 11 and 12), in which the right nucleus was destroyed and approximately 60 per cent of the left nucleus was eliminated. The known lateral and dorsal fiber connections of the left nucleus, including the pallidohypothalamic fibers, were destroyed. It may, furthermore, be said that every cat in which the area of the ventromedial hypothalamic nucleus was destroyed became savage or showed a marked tendency toward savageness. In many of the cats with pronounced change in behavior which showed complete destruction of the ventromedial nucleus the only criterion which prevented classification of the behavior as savage was the fact that they would not attack inanimate objects. They would, however, savagely attack other cats or man. The true "savage" cats would attack anything when irritated. The animals of the group with pronounced change in behavior in which part of the nucleus hypothalamicus ventromedialis remained (cats P23, P35 and P41) were the least savage in this category; while they never responded favorably to petting, they frequently retreated threateningly instead of taking an aggressive attitude toward the observer. Not enough data were available on the behavior of cat DI102 to determine the exact degree of savageness it manifested.

In some of the savage animals the lesions were highly restricted and specific, as in cat P20 (fig. 13). Of course, when the nucleus hypothalamicus ventromedialis was destroyed, all the pallidohypothalamic fibers entering it were also eliminated or they were necessarily indicated as such in the table. Unless the nucleus was not completely destroyed, as in cat P42, the two structures must be considered as a unit. It is perhaps significant that in savage cat P42 the pallidohypothalamic fibers were eliminated, and in most of the cats showing pronounced change in behavior with incomplete destruction of the ventromedial nucleus this fiber system was severely damaged. A neighboring structure, the fornix column, was often affected in the cats with decided change in or savage behavior. However, in some cats it escaped, while in the animals showing normal behavior or slight changes in behavior it was sometimes destroyed. These observations tend to eliminate the fornix from consideration as a factor the loss of which contributes to "savageness." Figures 13 (cat P20), 14 (cat P29) and 15 (cat P31) illustrate hypothalamic lesions associated with savageness.

Klüver and Bucy [45] found that in monkeys the removal of both temporal lobes, including the uncus and the greater part of the hippocampus, produced notable changes in emotional behavior in the sense that the motor and vocal reactions generally associated with anger and fear were not exhibited.

Various cortical areas were destroyed in some cats in this series of experiments to determine whether such lesions would be followed by addi-

tional alterations in affective behavior. Cat P20 was one of the animals treated in this manner, and the effect of lesions of the frontal lobe is illustrated by the continuation of the protocol begun in the preceding section.

The convalescence was marked by ataxia, motor difficulty and loss of postural reactions. There were no definite cataleptic symptoms. Although the cat frequently slumped to the floor in an awkward position, with her legs sprawled under her body, she did not remain stationary in any fixed position while standing
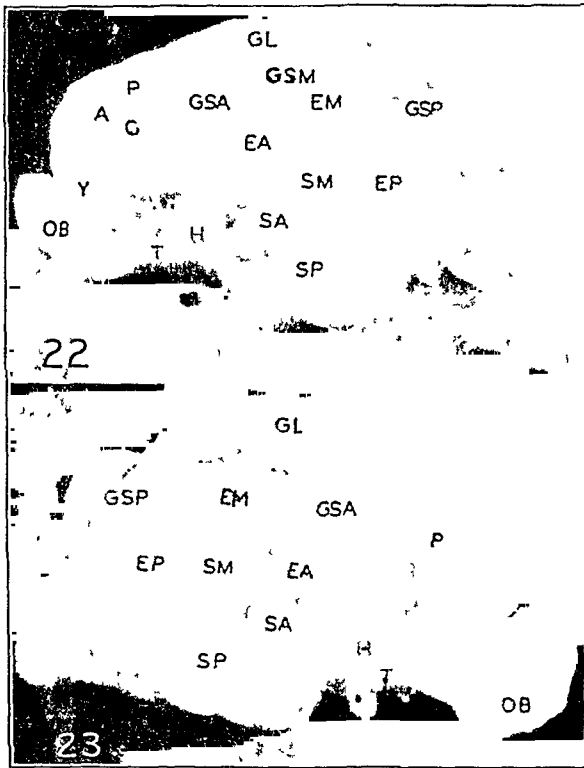
Figs. 22-23.—22, photograph of the left side of the normal brain of a cat.

In this figure and in figures 22 to 29, the following abbreviations indicate the gross structures: *A*, gyrus sigmoides posterior; *C*, gyrus coronalis; *EA*, gyrus ectosylvius anterior; *EM*, gyrus ectosylvius medius; *EP*, gyrus ectosylvius posterior; *GL*, gyrus lateralis; *GSA*, gyrus suprasylvius anterior; *GSM*, gyrus suprasylvius medius; *GSP*, gyrus suprasylvius posterior; *H*, gyrus orbitalis; *OB*, olfactory bulb; *P*, gyrus sigmoides posterior; *SA*, gyrus sylvius anterior; *SM*, gyrus sylvius medius; *SP*, gyrus sylvius posterior; *T*, olfactory tract, and *Y*, gyrus proreus.

23, photograph of the right side of the brain of cat P20. In this cat the gyrus proreus was removed, and the following gyri were damaged: The right gyrus sigmoides anterior was removed, and the rostral half of the left gyrus was ablated, with extensive damage to the part remaining; the gyrus sigmoides posterior was damaged rostrally on both sides; there were slight damage bilaterally to the rostral portion of the genual gyrus, damage to both coronal gyri and slight damage to the rostral end of the left lateral gyrus. The left olfactory tract sustained a slight incision dorsally.
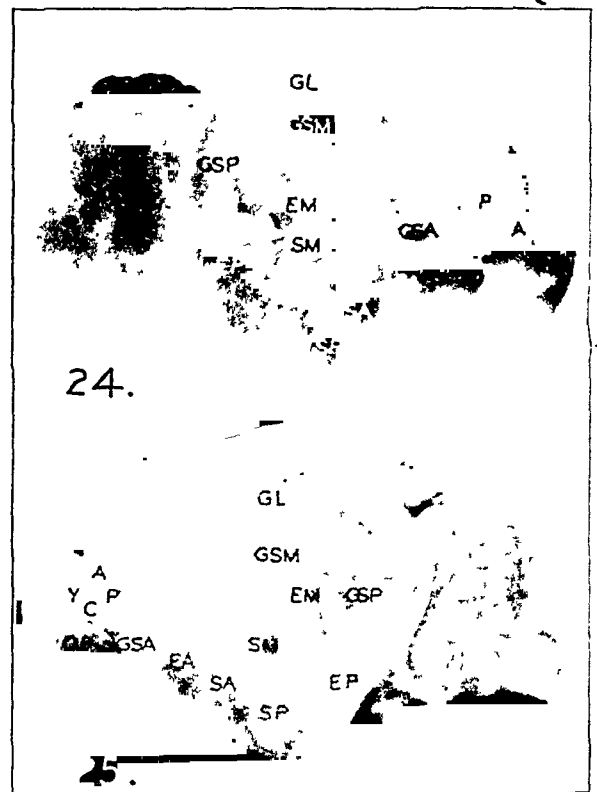
Figs. 24-25.—24, photograph of the right side of the brain of cat P31. In this cat, an attempt was made to damage the temporal region, in view of the observation by Klüver and Bucy [45] of a taming effect of such lesions in monkeys. The auditory projection area was therefore cauterized. As already mentioned, no change in emotional reactivity resulted in this experiment. On the right side, the anterior third of the cortex, the longitudinal part of the gyrus lateralis and the gyri adjacent to the inferior half of the lateral sulcus were undamaged. All other gyri on the lateral surface were damaged more or less, with the greatest destruction noticeable about 16 mm. dorsal to the ventral surface of the pyriform lobe.

25, photograph of the left side of the brain of cat P31. On the left side, all the gyri behind the posterior sigmoid gyrus showed varying degrees of damage or destruction. The area of greatest damage was in the gyrus ectosylvius medius. On both sides the damage affected not only auditory but visual areas, and sensory defects in these modalities were noticeable.

45. Klüver, H., and Bucy, P. C.: Preliminary Analysis of Functions of the Temporal Lobe in Monkeys, Arch. Neurol. & Psychiat. **42**:979 (Dec.) 1939.

or when lying on her back in a trough. This cat progressively regained a fair degree of control of her muscles. She did not eat of her own volition for two weeks, and then would not eat when the observer was present. Before this she was fed by tube. On eight

The following protocol is that of a typical savage cat:

CAT P20.—During the preoperative period, this cat, a mature, gray female, was very friendly although somewhat shy. She did not run after other cats and sought out the observer only when hungry; otherwise, she was content to stay in the background. When she was approached, she showed all the friendliness that cats can display. She was in estrus from April 16 to 20. During this time she sought out male cats in the usual manner and was not so shy with attendants. After this period she returned to her usual shy but friendly behavior. When aggressive cats attacked her, she cowered back, with ears flattened, but was never observed to make an aggressive move. When she was roughly handled, she tried to escape but did not use her claws and appeared bewildered. She did not play with other cats and only occasionally played with a ball or string. Her coat was well kept. She was slow and dainty in consuming her food.

On May 4, this cat was operated on while under pentobarbital anesthesia. She was then placed in a warm chamber (31 C.) for two days. On May 6 she licked her lips and growled when handled. She was placed in a leather harness to facilitate handling without danger to the observer; at this time she struck at the observer and was restless. On May 7 she ate her food. Before feeding she could be touched, but thirty minutes later she growled, hissed and struck with unsheathed claws when approached. On May 8 she assumed a typical "Hallowe'en stance," with ears flattened against the head, when any one approached her cage. She growled, hissed and struck if one attempted to touch her. She consumed all her food within fifteen minutes after it was placed in her cage. Before operation she often took several hours to finish her food. On May 9 she ate ravenously. Later she struck at the cage door when the observer approached her cage. Although she did not fly into a rage when food was placed in her cage, she could not be touched or petted. She showed marked horripilation and mydriasis when aroused and attacked anything which approached her. Usually when irritated she micturated several times and defecated until eventually nothing but mucus was passed. The volume of this mucus seemed abnormally large and may have indicated excessive secretion. Attempts to induce her to play with a ball or string brought on a fit of rage. When she was turned loose in a room with other cats, she attempted to retreat and remain in the background but attacked in a savage manner any cat that touched her. During the period from May 10 to September 21, this cat remained in a savage state. She was not observed in estrus during that time.[37]

On September 22, cat P20 was operated on while under anesthesia induced with pentobarbital, and all the neopallium anterior to the midregion of the posterior sigmoid gyrus was ablated on both sides.

[37]. Although no special effort was made to test the sexual behavior of the cats in this series, not one of the animals which showed notable change in behavior or became savage was observed to display the slightest interest in one of the opposite sex.

EFFECTS OF SECONDARY LESIONS AND ABLATIONS

Some clinical observers (Moniz and Lima[38]; Penfield and Evans[39]; Messimy,[40] and Freeman and Watts[41]) have reported the effects of frontal lobectomy and lobotomy on psychoses and neuroses, especially in persons suffering from manic or depressive states. According to the general theory on which such operations are based, these lesions eliminated malfunctioning areas and allowed other parts of the brain to recover their normal functions. Freeman and Watts[41] expressed the belief that ". . . prefrontal lobotomy acts upon the psychoses by removing more or less completely the emotional component with which the ideas are endowed . . . " and that this operation " . . . radically alters the personality of the individual in that it makes him no longer interested (affectively observant) in himself, either as an integrated collection of organs, or as a unit of society. . . ." Opinions vary as to the value of this procedure. The exact mechanism whereby ablation or lobotomy produces such changes is undetermined. Nevertheless, the frequency of occurrence of euphoria and loss of memory for recent events following these operations, as in Brickner's case (Brickner[42]), suggested the possibility that similar operations in the savage cats might alter their observed behavior. Jacobsen[43] and Jacobsen, Wolfe and Jackson[44] reported that, in addition to these two principal effects noted in man, monkeys and chimpanzees after frontal lobectomy no longer displayed the "temper tantrums" which difficult problems evoked in certain normal animals.

Removal of the frontal areas in cats has usually been observed to have little effect on emotional expression (Magoun and Ranson[26]; Barris[27]; Spiegel, Miller and Oppenheimer[25]).

38. Moniz, E., and Lima, A.: Symptômes du lobe préfrontal, Rev. neurol. **65**:582, 1936.

39. Penfield, W., and Evans, J. P.: The Frontal Lobe in Man: A Clinical Study of Maximum Removals, Brain **58**:115, 1935.

40. Messimy, R.: Les effets chez l'homme des lésions préfrontales, Ann. de méd. **45**:321, 1939.

41. Freeman, W., and Watts, J. W.: The Radical Treatment of the Psychoses and Neuroses, Dis. Nerv. System **3**:6, 1942.

42. Brickner, R. W.: Intellectual Functions of the Frontal Lobes: A Study Based upon Observations of a Man After Partial Bilateral Frontal Lobectomy, New York, The Macmillan Company, 1936.

43. Jacobsen, C. F.: The Effects of Extirpations on Higher Brain Processes, Physiol. Rev. **19**:303, 1939.

44. Jacobsen, C. F.; Wolfe, J. B., and Jackson, T. A.: An Experimental Analysis of the Functions of the Frontal Association Areas in Primates, J. Nerv. & Ment. Dis. **82**:1, 1935.

handled, as for hypodermoclysis, they would rapidly chase the observer about the room and attack him when he stopped.

With 1 exception, cat P23 (fig. 27), these cats showed no definite change in emotional status. After the ablation of the neopallium anterior to the ansate sulcus, cat P23 did not show mydriasis, horripilation or the threatening retreat which she exhibited after the operation on the hypothalamus; however, she never responded favorably to petting and still growled and hissed when handled. She exhibited hyperactivity to a notable degree, bumping and pushing into the corners and sides of her cage. She opened the incision the second day after the operation. Her condition rapidly deteriorated, and she was killed when in a dying condition, on the fourth postoperative day. Cat P31 (figs. 24 and 25), despite extensive damage to the auditory and visual areas of the brain, with resulting deficiencies in hearing and vision, attacked viciously when touched and growled for several minutes after such a contact.

Although extensive damage to the olfactory system in cat P28 (fig. 28) caused such loss of the sense of smell that he could not tell the difference between food and a mixture of sawdust and water, there was no alteration in the behavioral status. A normal cat in which the olfactory bulbs were removed likewise showed no change in emotional expression. Both these cats when hungry would take bites of sawdust moistened with water in the same manner in which they partook of food. Neither cat swallowed the sawdust, and both soon spat it out, but they were unable to distinguish between it and food of similar appearance before they took portions of it into the mouth. Normal cats were always able to differentiate between the two; at least, they never tried to eat the sawdust mixture.

Several cats in the hypothalamic series had shown normal behavior, or only slight change, despite destruction of the fornices. The fact that Spiegel, Miller and Oppenheimer [25] observed pronounced rage reactions in cats after placement of lesions in the fornices, with involvement of the septum pellucidum anterior to the columns of the fornices, suggested the desirability of performing similar operations on cats which had shown a continuation of normal behavior, or only a slight change. Such lesions were placed in cat P32. No behavioral changes followed, although the fornices were extensively damaged and the septum pellucidum was largely destroyed just anterior to the columns of the fornices. A similar operation on cat P33 (with normal behavior) resulted in total destruction of the fornices, with extensive involvement of the septal structures

of this area. Although this cat died on the second postoperative day, she was able to respond favorably to petting, and no behavioral change was noted. Also, cat P27 (with a slight change in behavior), after extensive destruction of the fornices with involvement of the septal area, did not show the slightest degree of change in the direction of savageness. If anything, she became less irritable and purred almost constantly when in the observer's presence.

Additional lesions were placed in this area in cat P29 (savage); and, although the fornices had been destroyed by the primary lesions, the damage to the septum pellucidum did not cause any further alteration in behavior. She lost none of her savageness.

Unless otherwise noted, all cats with secondary lesions were killed after a period of survival adequate for behavioral studies.

COMMENT

The correlation of the destruction of the area of the ventromedial hypothalamic nucleus with the development of a savage type of behavior is a new observation. Ingram [31] had observed such changes in the personalities of cats following lesions in this general area, but the destruction was not confined to such relatively narrow limits. Alpers [14] reported the case of a patient who was subject to periods of excitement bordering on rage. Microscopic examination revealed that most of the medial hypothalamic nuclei were severely damaged. There have been similar reports by other clinical observers, but pathologic lesions of the sort affecting the hypothalamus are rarely restricted enough for purposes of precise localization.

The destruction of thalamic structures or unilateral lesions in the hypothalamus in the present series did not result in the development of "savage" behavior. These observations differ from those of Kessler,[30] who described aggressive activity in cats following unilateral destruction of the thalamus or the hypothalamus. Kessler stated: "An unusual lability of the subject's emotional display . . ." resulted from unilateral diencephalic lesions "placed under more or less direct vision by following the stump of one optic nerve to the chiasmal region." His observations were not supported by detailed histologic study, and the placement of the lesions, according to his description, was vague.

Fulton and Ingraham [47] reported emotional disturbances following lesions placed in the base

47. Fulton, J. F., and Ingraham, F. D.: Emotional Disturbances Following Experimental Lesions of the Base of the Brain (Pre-Chiasmal), Am. J. Physiol. 90:353, 1929.

occasions she received subcutaneous injections of 100 cc. of sterile isotonic solution of sodium chloride. During these injections she struggled violently and for several minutes had good control of her facilities for attacking the observer, being able to strike repeatedly. In the absence of this intense stimulation, she would strike at the observer when approached, but could not unhook her claws for several seconds or until aroused to another effort. Despite this motor difficulty, there was no abatement of savageness, and she never responded favorably to petting; in fact, she growled and assumed an offensive position on the approach of a person or of other cats. On October 9

stroyed. Figure 22 is a photograph of a normal cat brain, shown for purposes of comparison. The degree of motor involvement varied from cat to cat. All the animals seemed to become exhausted after a relatively short period of intense activity. Some showed restlessness and hyperactivity. Cats P18 and P25 had a conspicuous tendency to be attracted by visual stimuli —following a moving object but wandering past or stopping when the object followed came to rest (Smith[46]). However, shortly after being
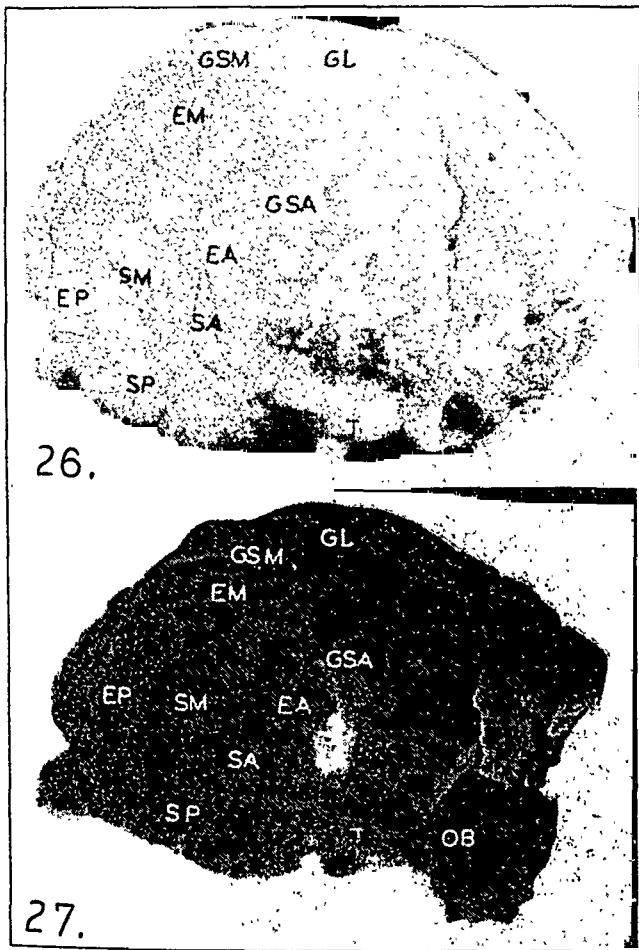
Figs. 26-27.—*26*, photograph of the right side of the brain of cat P18. In this cat, all structures anterior to the rostral end of the gyrus ectosylvius anterior were extirpated. The anterior surface of the remaining portions of the brain was necrotic and damaged.

27, photograph of the right side of the brain of cat P23. In this cat, all the neopallium rostral to the gyrus sylvius anterior was ablated or severely damaged. The olfactory bulbs appeared normal, but the superior surfaces of both olfactory tracts were damaged and eroded to a depth of approximately 2 mm.

the cat became so enraged when handled that it was impossible to test her postural reactions. She urinated, defecated and showed all the behavior pattern of a savage cat. She was then killed; the head was perfused with a dilute neutral solution of formaldehyde, and the brain was removed for examination. Figure 23 is a photograph of the brain of this cat, showing the extent of damage and ablation.

Similarly, various portions of the cerebral hemispheres of cat P31 (figs. 24 and 25), cat P18 (fig. 26), cat P23 (fig. 27), cat P28 (fig. 28) and cat P25 (fig. 29) were extirpated or de-
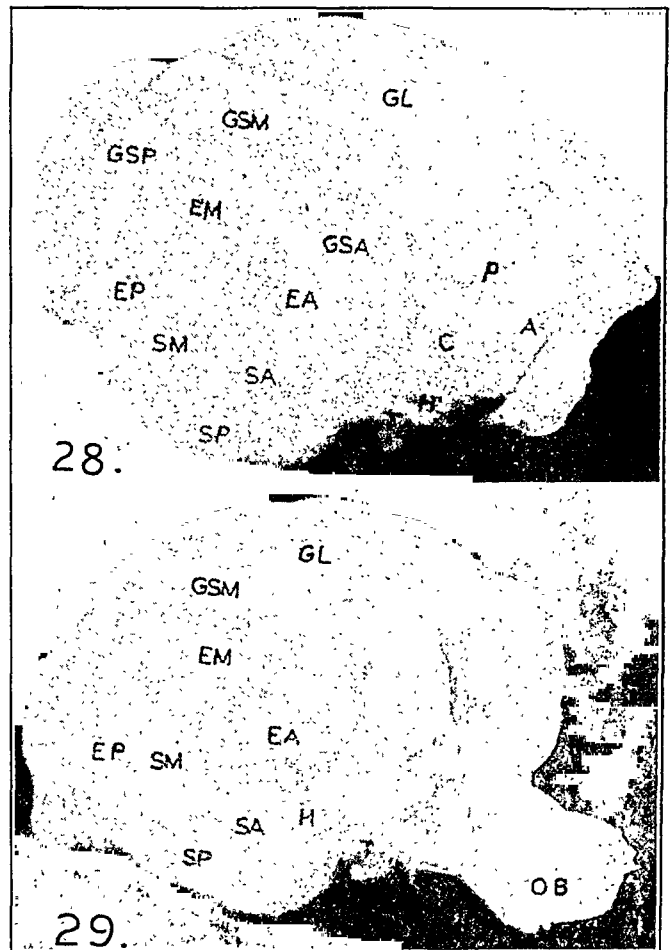
Figs. 28-29.—*28*, photograph of the right side of the brain of cat P28. The right olfactory bulb was removed and the corresponding tract removed rostral to the olfactory tubercle, with involvement of the tubercle. Most of the olfactory bulb and tract on the left side were removed, but the lateral third did not show complete degeneration. The rostral end of the anterior sigmoid gyrus was damaged.

29, photograph of the right side of the brain of cat P25. In this cat, the gyrus proreus and the gyrus sigmoides anterior were ablated. The gyrus sigmoides posterior was completely extirpated on the right side, but a small degenerated portion remained on the left. Laterally, all the neopallium rostral to the gyrus ectosylvius anterior was removed. The rostral ends of the remaining portions of the neopallial gyri were damaged, and there were several pits. An area of softening in the region of the medial longitudinal fissure extended back into the genu of the corpus callosum. Both olfactory tracts were damaged posterior to the bulb.

46. Smith, K. U.: Hyperactivity in the Cat After Ablation of the Frontal Lobes and Its Relation to Visually Controlled Aspects of Behavior, Psychol. Bull. **39**:493, 1942.

Brenner [50]) have reported definite pleasure reactions in such animals. Bard (Bard and Rioch [23]) described a preparation in which not only the neocortex but the hippocampus and the pyriform lobe were removed on each side. This cat, in addition to purring, arched her back and made pleasure movements with her forepaws when suitably stimulated. The savage cats in the present series never responded with the slightest sign of pleasure; and although they might be touched with safety before feeding, they could not be trusted. They frequently attacked the observer at this time. Furthermore, while they ate avidly, they did not display the normal signs of enjoyment of their food.

Despite these differences in behavioral patterns, the responses of the two types of animals showed definite characteristics of emotional reactivity suggestive of rage. Normal emotion is undoubtedly impossible in both the "sham rage" animals and the "savage" animals. Any statement as to the relative importance of either the cortex or the ventromedial hypothalamic area with respect to each other and to the organism as a whole would be sheer speculation. If the hypothesis of "release" is accepted, it must be acknowledged that the structures inhibited have not yet been localized. Possibly they are located at several levels. The work of Bard [22] and that of Ranson [29a] suggest the possibility that at least part of the excitatory area may be situated in the hypothalamus. Lesions dorsolateral to the mamillary nuclei changed wild monkeys into tame ones. Bard expressed the opinion that the essential area was in the caudal part of the hypothalamus. Keller,[51] on the other hand, reported rage reactions after elimination of all brain tissue rostral to the midbrain. This observation makes necessary the investigation of excitatory areas other than those in the diencephalon. It will be recalled, however, that Bard denied that the picture of sham rage in its entirety can be obtained when the caudal part of the hypothalamus has been lost. The question of independent inhibitory activity by either the cortex or the ventromedial hypothalamic nucleus cannot be answered with certainty. Undoubtedly, the cortex inhibits the activities of subcortical structures, but the mechanism of this inhibition with respect to emotional behavior and the pathways through which it is accomplished have thus far only been postulated. Frontal areas have been extirpated

without production of release phenomena (Magoun and Ranson [26]; compare Bellows and Van Wagenen [52]). Destruction of auditory areas of the cortex in monkeys resulted in suppression, rather than release, of rage phenomena (Klüver and Bucy [45]). Such operative intervention in the savage cats in this series caused no observable differences in the behavioral status.

It is questionable whether the lesions in the ventromedial hypothalamic nuclei interrupt inhibitory fibers from the cortex. The identity of such fibers in this region has not been properly established. Fibers of the periventricular system which connect the thalamus and the hypothalamus, and which are possibly a part of a corticohypothalamic system, are present here; but their activities have not been determined. There is no reliable anatomic evidence for concentration of such fibers in this particular area.

There is as yet inadequate information as to whether the destruction of afferent or efferent fibers related to this area has the same effect as destruction of the nuclei themselves. For instance, in cat P6, afferent fibers passing through the anterior hypothalamic area were destroyed without apparent effect. Also, in cat P1, the ventromedial portions of the thalamus were bilaterally involved in such a way that a great part of the thalamohypothalamic fiber system, as well as many pallidohypothalamic fibers, were destroyed without development of savage behavior. The only evidence on the positive side is suggested by the results in a single savage cat (P42), in which part of the ventromedial nucleus remained but in which the pallidohypothalamic and other dorsolateral connections were destroyed along the entire length of the nucleus. Further work on this score is indicated.

The part played by the area in question (whether the nucleus itself as a topographic entity or other elements located here) in relation to the activities of the nervous system as a whole in establishment of behavior patterns awaits analysis. Can it be that this area has an interlocking activity affecting the functions of the cortex? At any rate, present evidence indicates that in this restricted area in cats there is a nodal point at which the pathways mediating benign and malevolent behavior cross. When its activities are lost, behavior in cats reverts to an unrestrained savage, defensive and antisocial type.

50. Rioch, D. M., and Brenner, C.: Experiments on the Corpus Striatum and Rhinencephalon, J. Comp. Neurol. 68:491, 1938.

51. Keller, A. D.: Autonomic Discharges Elicited by Physiological Stimuli in Midbrain Preparations, Am. J. Physiol. 100:576, 1932.

52. Bellows, R. T., and Van Wagenen, W. P.: The Effect of Resection of the Olfactory, Gustatory and Trigeminal Nerves on Water Drinking in Dogs Without and With Diabetes Insipidus, Am. J. Physiol. 126: 13, 1939.

of the brain rostral to the chiasm. This often cited observation was not supported by histologic delimitation of the structures involved. Spiegel, Miller and Oppenheimer [25] reported:

. . . lesions encroaching upon the olfactory tubercles or isolated lesions of the tubercles were followed by distinct rage reactions (6 cases), particularly if the lesions extended medialward to the septum pellucidum.

Extreme rage reactions were obtained after transection of the fornices and damage to the septum pellucidum. These authors also observed somewhat paradoxic results after bilateral injury to the amygdaloid nuclei; both rage reactions and cataleptic symptoms followed such lesions. Their lesions were illustrated by gross cross sections, without apparent histologic analysis.

Microscopic scrutiny often reveals damage not apparent on gross examination. As an example, cat DI87 (table 4) had a section of the hypophysial stalk. This structure has no logical connection with behavior changes of the type dealt with here; nevertheless, the cat became savage, with additional psychopathic manifestations. Gross examination revealed no significant damage other than section of the stalk. However, microscopic study revealed an area of softening in the region of the tuber which destroyed the ventromedial nuclei and other structures. This injury was produced either inadvertently or from damage to vascular structures. Other cats subjected to section of the stalk retained a normal type of behavior. Cat DI165 (table 1) exemplified the usual result of such an operation, and microscopic examination of the brain of this cat revealed that only the supraoptic nuclei and the supraopticohypophysial tracts were degenerated.

While lesions destroying the region of the ventromedial hypothalamic nuclei are associated with the development of a savage type of behavior, one must be reserved in assigning to this specific cell group a function in the maintenance of normal, restrained, tame behavior. It must not be forgotten that this is an area of passage of fibers, and it is not impossible that there may be here a converging point for fibers which in other regions are scattered, so that relatively few are susceptible to destruction by restricted lesions. On the other hand, it is not impossible that in this area, in cats at least, important integrative mechanisms of an inhibitory nature exist.

The mechanism whereby the destruction of the region in question produces the loss of friendliness and the development of savageness is obscure. The fact that the condition persists long after convalescence and organization of the in-

volved areas eliminates irritation as a causative agent. Evidence that electrical stimulation of this area produces euphoric or friendly behavior is almost nonexistent. It is perhaps significant in this respect that Gibbs and Gibbs,[48] in stimulating scattered areas throughout the brains of 400 cats, obtained purring in response to weak stimulation of the infundibular region in 3 animals. On the other hand, significant results of other sorts have been obtained with stimulation in hypothalamic areas other than the ventromedial nuclei. Ranson [29a] reported that he and his associates were successful in eliciting many of the manifestations of rage by stimulation of the region occupied by the medial forebrain bundle in the lateral part of the hypothalamus. Negative results were obtained by stimulation of the surrounding parts of the brain, such as the thalamus, the internal capsule, the septum, the infundibular stalk and the extrahypothalamic gray matter surrounding the fornix, or the fornix itself, except where this fiber bundle penetrated the lateral hypothalamic area. No rage effects were observed on stimulation of the medial portions of the hypothalamus. It should be added, however, that knowledge of hypothalamic function, as indicated by stimulation experiments, may be extended or modified as different technics are applied.

Rage reactions have been demonstrated by Bard and others after decortication and high decerebration. These responses have been explained on the basis of release phenomena. The "sham rage" exhibited by decorticate animals differs in certain respects from the rage reactions shown by the savage cats in the present study. Whereas the decorticate animals displayed these reactions only during the time in which outside stimuli were active, the cats in this series continued to respond for a considerable period after cessation of the stimulus. The attacks of the savage cats were well directed, unlike the blind fits of emotional display elicitable in the decorticate animals. For instance, after the destruction of the ventromedial region in cats P5 and D18, these animals would not attack inanimate objects, even avoiding a stick held by the observer in order to attack the latter's hand or arm. The emotional reactions of decorticate cats are not limited to displays of rage, for several investigators (Rioch [49]; Bard and Rioch [23]; Rioch and

48. Gibbs, E. L., and Gibbs, F. A.: A Purring Center in the Cat's Brain, J. Comp. Neurol. 64:209, 1936.

49. Rioch, D. M.: Certain Aspects of the Behavior of Decorticate Cats, Psychiatry 1:339, 1938.

The brains were examined histologically. This series of brains was supplemented by specimens from another group of 28, the behavior of which had been noted after production of hypothalamic lesions for other purposes. Anatomic analysis showed that destruction of the region of the nucleus hypothalamicus ventromedialis was invariably associated with savage behavior of an extreme type, with complete loss of any friendly attitude. In many cases the lesions were highly restricted. Partial destruction of this nuclear area in many instances was associated with varying degrees of affective change. Evidence is not available to indicate whether the nucleus itself is the controlling factor or whether other factors participate.

CONCLUSIONS

Lesions destroying the immediate region of the ventromedial hypothalamic nuclei in cats result in loss of favorable response to friendly treatment and handling and in change from a friendly behavior pattern to one of malevolence and savageness, to a marked or an extreme degree. Attempts to produce this result by means of other lesions failed. Efforts to modify this behavior pattern by lesions or ablations of higher regions of the brain have also thus far essentially failed. The details of the mechanisms controlling or permitting the change are obscure.

Dr. W. R. Ingram advised in the carrying out of this experiment.

State University of Iowa College of Medicine.

The matter of corticohypothalamic relations remains a problem. Masserman [53] observed that cats were unable to adapt to direct stimulation of the hypothalamus in conditioning experiments and concluded that the hypothalamus may not be the "dynamic source or the seat of experience of affective states." Nevertheless, some experiments have indicated that destruction of the hypothalamus may alter the activity of the cortex. Grinker and Serota [8] noted temporary abolition of the cortical potentials following destruction of the hypothalamus in cats. Obrador Alcade [54] reported no return of cortical potentials following destruction of this area in acute cat preparations, and Kennard [55] observed that the bilateral destruction of the hypothalamus abolished or diminished the pattern of the cortical potentials in chronic monkey preparations. On the other hand, Morison, Finley and Lothrop [56] stated that in their experiments they found nothing to suggest an intimate relation between activity of the cortex and that of the hypothalamus. More work is necessary to place knowledge of corticohypothalamic relations on a sound basis.

A word must be said in regard to lesions involving olfactory structures. The part played by the olfactory sense in primitive behavior is well known. In my experience removal of the olfactory bulbs in normal cats and in cat P28 (with variable behavior) had no effect on emotional display. Similar results have been reported by other investigators (Spiegel, Miller and Oppenheimer [25]). On the other hand, Bellows and Van Wagenen [52] reported that the "believed" loss of olfactory sense due to injury of the olfactory tracts was associated with fear, rage or even maniacal behavior in dogs. It is not apparent that a careful histologic study was made, and it is important to note that in performance of the operations the frontal lobes were removed and various parts of the hypothalamic structures damaged. An account of the condition of the hypothalamus in these dogs would have been interesting. Although Spiegel, Miller and Oppenheimer [25] reported rage reactions following destruction of the fornices with involvement of the septum pellucidum in cats, the results of such lesions in the present experiments were negative. Dott and associates [11] noted no symptoms referable to section of the fornices and incision of the lower part of the septum pellucidum in their patients. Spiegel, Miller and Oppenheimer [25] reported rage reactions following bilateral lesions in the olfactory tubercles, especially when the lesions extended medially into the septum pellucidum. The mechanism of this effect needs further investigation.

A word should perhaps be added with regard to the avid appetite and tendency to gain in weight of many of the savage cats. My observations on the score of obesity were not sufficiently controlled with respect to variations in diet, metabolic factors and activity to contribute materially to the problems involved in the question of hypothalamic obesity. It is significant to record, however, that cats with hypothalamic lesions may become abnormally fat, an observation which adds the cat to the species in which the phenomenon has previously been noted. It is also of interest to note that Hetherington [57] stated the belief that obesity-producing lesions in rats are in the region of the ventromedial nucleus and that the lesions in the series of Brobeck and associates [34] were in the same vicinity. Further work on this score is indicated.

SUMMARY

The behavior of 42 selected, tame, friendly cats was studied for several weeks. In addition to observation of each animal's response to everyday environmental contacts, such as reactions to other cats, behavior toward the observer, feeding habits and cleanliness, the response to nociceptive electrical stimuli was noted. Bilateral lesions were then placed in the hypothalamus with the aid of the Horsley-Clarke stereotaxic instrument. Daily postoperative records of behavior were kept in a manner similar to that for the preoperative observations. Of the 42 cats, 13 remained friendly; 8 showed slight irritability; 7 displayed pronounced savageness; 10 became very savage, and 4 exhibited variable behavior in that their moods of friendliness alternated with periods of aggressiveness. Additional lesions were placed or ablations of various cortical regions were performed in 11 of these cats to determine whether such intervention would ameliorate savageness or produce rage reactions in the cats which had retained their normal friendliness.

53. Masserman, J. H.: Behavior and Neurosis, Chicago, University of Chicago Press, 1943.

54. Obrador Alcade, S.: Effect of Hypothalamic Lesions on Electrical Activity of Cerebral Cortex, J. Neurophysiol. 6:81, 1943.

55. Kennard, M. A.: Electroencephalograms of Decorticate Monkeys, J. Neurophysiol. 6:233, 1943; Effects on Electroencephalogram of Chronic Lesions of Basal Ganglia, Thalamus and Hypothalamus of Monkeys, ibid. 6:405, 1943.

56. Morison, R. S.: Finley, K. H., and Lothrop, G. N.: Spontaneous Electrical Activity of Thalamus and Other Forebrain Structures, J. Neurophysiol. 6:243, 1943.

57. Hetherington, A. W.: Non-Production of Hypothalamic Obesity in the Rat by Lesions Rostral or Dorsal to the Ventromedial Hypothalamic Nuclei, J. Comp. Neurol. 80:33, 1944.

shielding is required to take these tracings, and in general they can be obtained under all conditions in which electrocardiograms can be taken. If the potential can be suitably amplified and recorded on a cathode ray tube, as has been done in many of the experiments reported in this paper, more detailed observations as to its shape and duration can be made (fig. 2). The size of normal action potentials from muscles of the extremities is generally more than 5 microvolts (fig. 1). In most electrocardiographs the sensitivity can be sufficiently reduced to photograph such potential changes. It is necessary to calibrate the sensitivity of the recording instrument when records are made, so that the voltage of the potentials can be compared with those taken during subsequent periods of observation and alterations due to change in sensitivity of the recording apparatus recognized.

Stimulation.—The stimulating current for the motor nerve is applied by breaking the current flow in the primary of an induction coil with a Morse key or any suitable type of contact breaker. No appreciable stimulation occurs when the key in the primary circuit is closed, even when the subsequent "break" shock causes maximal stimulation of the motor nerve. The key in the primary circuit should be pressed down firmly and then released suddenly after the motor of the electrocardiograph is started.

In order to apply maximal stimuli to the motor nerves through the skin, high voltages may be required. These depend on the ratio of the windings of the primary coil to those of the secondary coil. Coils for strong stimulation generally have an iron core in the primary circuit. Strength of stimulus can always be varied by changing the relative position of the primary and the secondary coil to each other. The standard induction coils available in physiologic laboratories can be used for the purpose. Two stimulating electrodes lead from the secondary coil to the patient. One "indifferent" electrode consists generally of a large copper or zinc plate, about 3 by 5 cm., which makes contact with the patient's extremity about 10 to 20 cm. above the point along the nerve to be stimulated. The area of application should be rubbed with electrode paste, and a piece of cotton wool soaked in saline solution may be placed between the skin and the copper plate. To insure good contact, the electrode is fixed by a bandage or a rubber band.

The second stimulating electrode consists of a small round metal disk (1 cm. in diameter) attached to the end of a hardwood rod convenient for manipulation. Some gauze or linen may be tightly wound around the disk, in order to avoid any unpleasant burning sensation during stimulation. Before application of this localized stimulating electrode, the area of skin over the nerve should be cleaned and moistened with electrode paste and the cloth around the electrode soaked in saline solution. Stimulation itself does not cause pain, but the patient may be surprised by the mechanical response when the shock is first applied. He, therefore, should be told when to expect stimulation. During stimulation the extremity should be held in a relaxed, comfortable position. At the same time general movement should be prevented as far as possible, as excursions of the limb may result in the recording of movement potentials. As they always occur after the muscle action potential has been photographed, they do not interfere with the essential part of the recording, but they do cause alteration of the base line. A thin

plaster shell provides a convenient support for the extremity from which the recordings are made. Several points along the limb can be lightly strapped to the support and excessive movement after stimulation easily avoided.

Points of Stimulation and Areas of Recording.—In the upper extremity all the main nerve trunks are accessible to stimulation, and records can be made from nearly all the superficial muscle groups. However, for the most part, muscles which have parallel fibers seem to be better suited than others, giving more synchronous and larger action potentials. Generally, one electrode is placed over the muscle under investigation and the other over an inactive neighboring area or over the tendinous portion of the muscle under study.

Points of Stimulation: In many instances the nerve to be stimulated can be located by palpation. The optimal location for the stimulating electrode varies from one subject to another and can be determined only by repeated shifting of the position of the electrode on the skin over the nerve until a maximal response is obtained.

Ulnar nerve: This nerve can generally be found without difficulty in the area above the medial epicondyle and is easily palpated.

Median nerve: This nerve runs in the depth of the elbow on the medial side, where it lies behind the lacertus fibrosus and is separated from the elbow joint by the brachialis muscle. In the forearm it passes between the two heads of the pronator teres muscle. The best point of stimulation is generally found to be proximal to the lacertus fibrosus, just medial to the tendon of the biceps muscle.

Radial nerve: This nerve can be palpated over 2 to 3 cm. of its length, as it winds posteriorly from the medial to the lateral side of the humerus, between the medial and the lateral head of the triceps muscle. Repeated trials are usually necessary, as it is often difficult to find the exact point at which maximal stimulation can be obtained.

Common peroneal nerve: In the lower extremity this nerve is the most readily accessible. It can be stimulated behind the head of the fibula at the lateral side of the popliteal space. The knee must be bent to a varying degree, depending on the position and tone of the tendon of the biceps muscle. The correct position is easily determined, and maximal stimulation is not difficult to obtain.

Tibial nerve: Maximal stimulation of this nerve is frequently difficult, and only a few recordings have been made from the muscles which it innervates.

Areas of Recording: Ulnar nerve: When the ulnar nerve is stimulated, recording from the muscles of the hypothenar eminence, the abductor pollicis muscle and part of the flexor pollicis brevis muscle is possible. The abductor digiti quinti muscle is preferable, as synchronous action potentials are usually obtained if one electrode is placed about 2 to 3 cm. distal to its point of origin and the other at the end of the muscle or on the skin over the first phalanx of the fifth finger.

Median nerve: Of the muscles supplied by this nerve, the flexor carpi radialis is most suitable, as it is superficially situated on the volar surface of the forearm. Eight to 10 cm. distal to its point of origin is the area in which the skin electrode is usually placed. Satisfactory records can also be made from the thenar eminence.

MOTOR NERVE FUNCTION WITH LESIONS OF THE PERIPHERAL NERVES

A QUANTITATIVE STUDY

MAJOR ABNER M. HARVEY

MEDICAL CORPS, ARMY OF THE UNITED STATES

AND

S. W. KUFFLER

SYDNEY, AUSTRALIA

In a great variety of abnormalities of the lower motor neuron it is of importance to determine the localization and the extent of the injury. It is also valuable to obtain a reliable and quantitative estimate of recovery of function or of the effect of treatment. A simple test has been devised which consists of application of a maximal electrical stimulus to the motor nerve and of recording, through the skin, the action potential of the muscle. An ordinary induction coil is suitable for stimulation, and the resulting electromyogram can be recorded on an electrocardiograph or any standard type of amplifier. Tests of this kind have been performed at an Army general hospital with which we are associated on patients with a large variety of peripheral nerve lesions during the past two years. In the present paper it is intended to describe the apparatus in detail and to point out its usefulness as an aid in the diagnosis and in observation of the progress of motor nerve function in these patients.

The present method employs a different approach to the problem than the electrical aids which have thus far been used in the diagnosis and prognosis of nerve injuries. The latter procedures may briefly be summarized as follows:

1. The classic method of determining the "reaction of degeneration" by faradic and galvanic stimulation. No accurate quantitative data are obtainable by this method, and in cases of partial lesions the results may be difficult to interpret. .

2. Determinations of chronaxia and duration of strength. Significant results can be obtained only by plotting the entire curve for the duration of strength (Rushton[1]), while measurements of chronaxia give only one point on the curve and are of little value in making a quantitative estimate of muscle function.

3. The electromyographic method, in which spontaneous or voluntary activity is recorded. This procedure is of use when the nerve is inaccessible to stimulation. Records of this type, when used in conjunction with records obtained by the method described in this paper, frequently provide additional information of value. Details of these various methods can be found in papers by Bauwens[2]; Watkins,[3] and Schwab, Watkins and Brazier.[4]

MATERIAL AND METHODS

Recording.—The electrodes used in recording are silver or solder cups (5 to 10 mm. in diameter) with a small opening at the top sufficiently large to allow the insertion of an 18 gage needle. They are similar to the electrodes employed in electroencephalographic recording. As good contact of these electrodes is essential, the skin should be thoroughly cleansed with ether or alcohol. At the point of contact it is advisable to scarify the surface of the skin with a needle in order to release a small amount of tissue fluid. This procedure reduces the interelectrode resistance and minimizes the stimulus artefact. A drop of electrode paste is then placed in the hollow portion of the electrodes; they are brought into contact with the skin and fixed there by the application of a thin layer of collodion over their surface. If, during the course of the observation, the stimulus artefact tends to increase, it is generally an indication that drying has occurred at the point of contact of the electrode with the skin, resulting in increased interelectrode resistance. This can easily be remedied by applying a drop of saline solution through the small opening in the top of the electrode. Care should be taken not to allow the spread of the solution over the skin in the area of the recording or stimulating electrodes. This may result in large escapes of current and in stimulus artefacts.

The simplest method of recording is by means of an electrocardiograph or electroencephalograph. No special

2. Bauwens, P.: Proc. Roy. Soc. Med. **34**:459, 1941.

3. Watkins, A. L.: Arch. Phys. Therapy **23**:76, 1942.

4. Schwab, R. S.; Watkins, A. L., and Brazier, M. A. B.: Quantitation of Muscular Function in Cases of Poliomyelitis and Other Motor Nerve Lesions, Arch. Neurol. & Psychiat. **50**:538 (Nov.) 1943.

1. Rushton, W. A. H.: Biol. Rev. **10**:1, 1935.

ation of reflexes, the differentiation of an organic and a hysterical abnormality was difficult. With a test available, such as the one described, partial loss of motor function can be detected, and the diagnosis may be made with more assurance.

A white man aged 26 was admitted with the complaint of weakness of the right hand, of sudden onset. There was no history of injury, and no obvious neuropsychiatric determinant was elicited.

The reflexes were normally active. Motor power was reduced in all the muscles of the hands to about one-half the normal, but the weakness was most noticeable in the extensors of the wrist and fingers.

The diagnosis on admission from the previous hospital was acute, peripheral, nonalcoholic neuritis of the right radial nerve, of undetermined cause.

Action potentials of the muscles supplied by the radial nerve were recorded in response to maximal electrical stimulation. The voltage of the potential from the right arm was the same as that obtained from the left (normal) arm, 6 microvolts (fig. 2 *A*).

simultaneously began to complain vigorously of pains about the precordial region. After a few weeks in the hospital he was returned to duty.

In each of these cases, as a result of studies of the action potentials, a diagnosis of psychoneurosis, hysteria, could be made with more certainty than would have been possible on the basis of clinical observation alone. The use of electrical stimulation and visual observation of the mechanical response may be of help when the complaint is that of complete loss of movement, but when partial loss of function is present a definite conclusion cannot be reached with certainty without the simultaneous recording of the action potential in the affected muscle.

Progress of Recovery.—The fact that these potentials in response to maximal stimulation of the motor nerve normally remain constant from day to day makes the method useful in following the progress of recovery in nerve lesions.
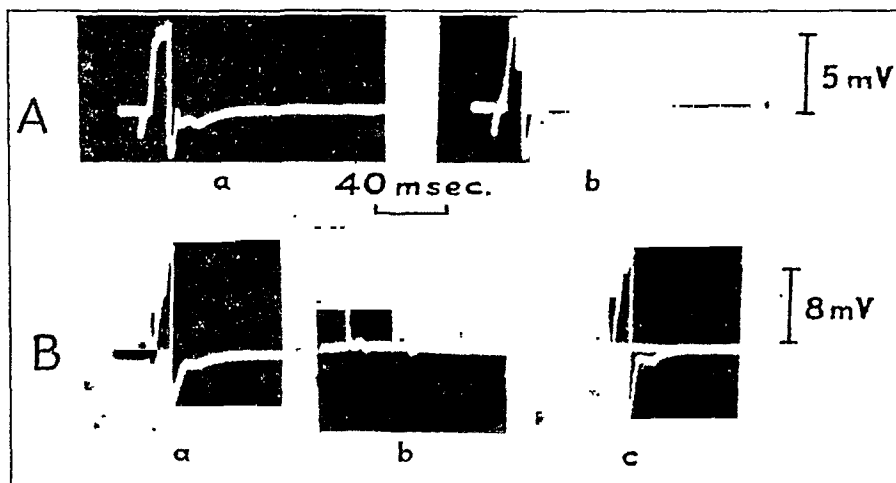
Fig. 2.—Muscle action potentials (cathode ray oscillograph) in response to maximal stimulation of the nerve (induction coil). (*A*) a case of hysterical paralysis: (*a*) normal side; (*b*) paralyzed side. (*B*) a case of traumatic neuritis of the radial nerve: (*a*) normal nerve (Nov. 1, 1943); (*b*) paralyzed nerve, two stimuli (November 1), and (*c*) paralyzed nerve (three weeks later).

The patient was referred to the psychiatrist for examination, and a diagnosis of psychoneurosis, hysteria, in an emotionally unstable personality was made. He improved rapidly under treatment and was returned to duty.

A Negro aged 21, a sergeant, was admitted in December 1943 because of "paralysis" of the right foot, with foot drop, which had been present since May 1943, when he dropped an unfused bomb on his foot.

Examination revealed no power in the dorsiflexor of the foot and toes and great reduction in function of the plantar flexors. The reflexes were normal.

Electrical stimulation of the peroneal nerve resulted in dorsiflexion of the foot, and the resulting action potentials from the tibialis anterior and the extensor digitorum longus muscles were equal in voltage to those obtained from the corresponding muscles of the normal leg.

The psychiatric consultant made a diagnosis of psychoneurosis, hysteria. After the electrical stimulation he was able to move the foot more effectively but

Figure 3 illustrates the curve of recovery in a case of peripheral neuritis.

A young man, after several months of residence in the tropics, suddenly had paralysis of the peroneal nerve with foot drop. The action potentials from corresponding muscles of the normal and the abnormal leg were compared at frequent intervals. The potentials from the normal muscles varied from 15 to 16 microvolts. The curve shows several points of interest. The potential remained at about 50 per cent of normal for almost three weeks, during which there was no change in the degree of weakness on clinical examination. During the following three weeks there was a steady increase in the size of the potential, which appeared for a brief period before demonstrable clinical improvement. The curve then flattened out, with the potential remaining 3 to 4 microvolts below that on the normal side. A detailed study of peripheral neuritis will be presented later

Radial nerve: Records are usually made from the brachioradialis and the extensor carpi radialis muscle when the radial nerve is stimulated. One electrode is generally placed several centimeters below the lateral epicondyle and the other in the region of the tendons of the extensors, at the wrist.

Peroneal nerve: In studies of this nerve, recording is done most frequently from the tibialis anterior muscle about 10 to 15 cm. below the patella and 1 cm. lateral to the edge of the tibia, but frequently more nearly synchronous and larger potentials are recorded about 3 cm. laterally, over the extensor digitorum longus and the peroneus longus muscle.

Satisfactory action potentials can be obtained from many regions other than those mentioned. The advisability of recording from a particular muscle frequently depends on the location of the nerve lesion and the set of nerve fibers involved. Thus, in certain cases of neuritis some muscles, although supplied by the same nerve, are more affected than others; and it is advisable to compare the potentials obtained from the various muscles innervated by the particular nerve under study. If small or complex potentials are obtained, better conditions for recording may be found after a slight shift of one electrode.
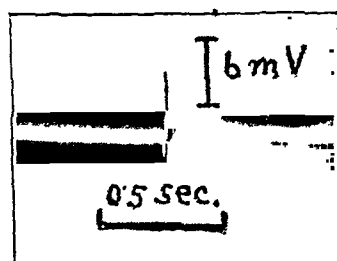
Fig. 1.—Action potential of the abductor digiti quinti muscle in response to maximal stimulation of the ulnar nerve.

Stimulation by induction coil, with recording on electrocardiograph.

During an actual experiment the following steps are taken in order to record the voltage of the muscle action potential in response to a maximal motor nerve stimulus:

The stimulating electrode is applied at various points along the course of the nerve. With practice, one can judge when the excitation of the nerve to a single stimulus is nearly maximal by observing the degree of movement in the contracting muscles and the deflection of the recording device. At this point, with the stimulating electrode held firmly in position, a record of the muscle action potential should be obtained. Without alteration in the position of the stimulating electrode, a second potential is then recorded after the strength of the nerve stimulus has been increased. If the first stimulus was maximal, the action potential in response to the second, and stronger, of the two stimuli will not have increased in size. Figure 1 shows a typical record obtained with an induction coil for the stimulation of the nerve and an electrocardiograph for the recording of the muscle action potential. This potential, of 6 microvolts, from the abductor digiti quinti muscle of a normal subject did not increase in size after a stronger stimulus was applied to the ulnar nerve.

RESULTS

If records of this type are taken under standard conditions, the potential in a normal muscle remains constant from day to day and over long periods (Harvey and Masland [5]). Comparison of the potentials from corresponding muscles on the two sides of the body rarely reveals a difference in the size of the potential of more than 15 per cent. Comparisons of this sort are indicated in the accompanying table in a variety of cases. It will be noted that although the potential values normally vary greatly for the different muscles, they are always within the same range on the two sides. In general, the voltage

Action Potential Voltages of a Number of Muscles in Response to Maximal Stimulation of the Motor Nerve

Muscle	Diagnosis	Action Potential, Microvolts	
		Right	Left
A. Normal Nerve			
Abductor digiti quinti......	Normal	6	7
Adductor pollicis brevis....	Normal	7	....
Abductor pollicis brevis....	Normal	18	16
Flexor carpi radialis.......	Normal	15	13
Flexor carpi radialis.......	Normal	12	....
Brachioradialis.............	Normal	11.5	11.5
Tibialis anterior...........	Normal	12.8	10.8
Extensor digitorum longus (leg)	Normal	12.3	12.0
B. Unilateral Nerve Lesions			
Abductor digiti quinti......	Peripheral neuritis (left)	5.2	2.4
Extensor digitorum communis	Hysterical wrist drop (left)	7.8	7.6
Brachioradialis.............	Traumatic neuritis (after recovery)	11.5	11.5
Brachioradialis.............	Traumatic neuritis	11.5	0.5
Tibialis anterior...........	Peripheral neuritis (right)	3.3	6.0
Tibialis anterior...........	Peripheral neuritis (left)	14.0	8.4
Tibialis anterior...........	Hysterical foot drop (left)	6.5	7.5
Extensor digitorum longus (leg)	Peripheral neuritis (left)	5.7	1.0

for any given muscle is within the same range, even in different persons. In the second part of the table the potentials recorded in a variety of clinical conditions are listed. Here, again, it is clear that the test is of value only when the normal and the abnormal muscle are compared or when the potential is recorded from the same muscle repeatedly over a considerable period.

The following cases serve to illustrate the variety of problems in which a study of this type is useful.

Hysterical Paralysis.—During the past year numerous cases of localized weakness of one extremity or a portion of one extremity were encountered in this hospital. In many of these cases the loss of motor function was incomplete, and in the absence of sensory changes or alter-

5. Harvey, A. M., and Masland, R. L.: Bull. Johns Hopkins Hosp. 68:81, 1941.

centric needle electrodes (Adrian and Bronk[6]), while synchronous discharges of muscle groups are easily detected by the use of skin electrodes. An extensive study of various types of spontaneous activity has been made by Denny-Brown and Pennybacker.[7] Further, recording of potentials in response to voluntary motor activity may be the only method available when the motor nerves are not accessible to stimulation.

When the information from these two methods of study and the one described in this paper are correlated, a more complete picture of the motor abnormality can be obtained than by the use of any one of them alone.

6. Adrian, E. D., and Bronk, D. W.: J. Physiol. 67:119, 1929.

7. Denny-Brown, D. E., and Pennybacker, J. B.: Brain 61:311, 1938.

SUMMARY

The method described here allows an accurate and objective evaluation of muscle function in cases of lesions of the peripheral neuromuscular system. Records can be made from most of the muscles of the extremities.

The motor nerve is stimulated by an induction shock, and by records of the muscle action potential the localization and extent of partial lesions of the nerve can be established. An ordinary induction coil is sufficient for stimulation, and the muscle action potential can be recorded by means of an electrocardiograph or any standard amplifying system.

The extent of nerve injuries and the course of various types of lower motor neuron involvement can be determined. The method is also useful in the diagnosis of hysterical muscular dysfunction.

Traumatic Neuritis.—Figure 2 *B* illustrates the results of study by this method in a case of neuritis due to pressure.

The patient awakened with complete paralysis of the radial nerve after sleeping on a train seat. Studies of the action potentials showed no function of the muscles in response to stimulation of the nerve. One week later improvement began, and the potential within three weeks became equal in size to that on the normal side. In this instance recovery was complete, in contrast to the result in the case illustrated in figure 3, and occurred much more rapidly.

In cases of temporary nerve paralysis of this type, as well as in those of partial nerve injury, in which it is desirable to know the exact degree of dysfunction, practical information can be obtained by the use of this method of study. Particularly in Army hospitals, a hysterical element

cent is rarely observed when corresponding normal muscles of the extremities are compared; (3) whenever a portion of a motor nerve is the seat of an organic lesion, the muscle action potential is reduced, and the potential returns toward normal as the function of the nerve increases.

The records represent the response of the muscles to a maximal stimulus of the motor nerve fibers innervating it, in contrast to other types of records, in which potentials are produced by spontaneous or voluntary activity.

Studies of the type described appear to be of special advantage in the investigation of cases of partial nerve injury, peripheral neuritis and an exaggerated weakness of muscle power. The presence or absence of innervation can be ascer-
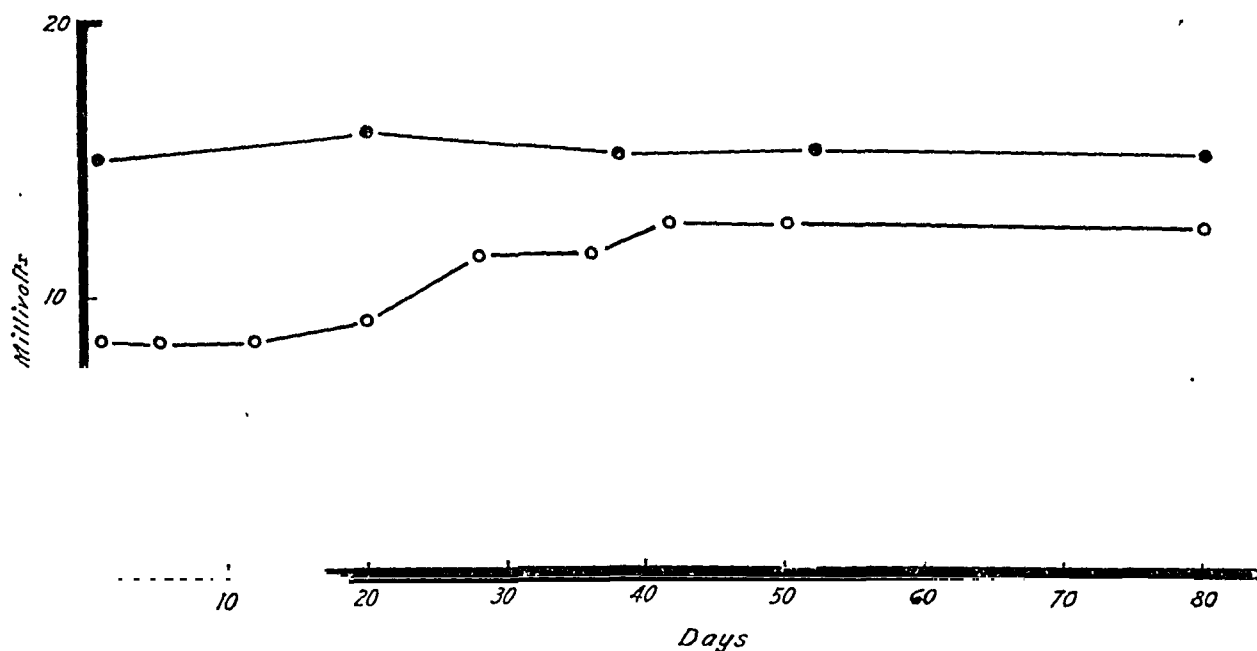
Fig. 3.—Recovery curve in a case of peripheral neuritis involving the peroneal nerve (line of hollow circles and dashes). The upper curve represents the variation in action potentials for the normal nerve.

may be superimposed in cases of partial nerve paralysis, and the extent to which this is present can be quickly ascertained if the action potential in response to maximal stimulation of the nerve is recorded.

COMMENT

Motor nerve function in various types of damage to the peripheral nerves, including peripheral neuritis, was investigated. The method which has been used represents a simplification of that described by Harvey and Masland [5] and offers many points of contrast to other types of electromyographic study. The following three points embodied in this type of study enable an accurate and objective estimation of nerve function: (1) When a maximal stimulus is applied to a motor nerve, the action potentials recorded under constant circumstances from the same muscle will show only slight variation over long periods; (2) a difference of more than 15 per

tained, and repeated observations will reveal the progress of recovery. This is of special interest in the early stages following injury. During the first few weeks motor nerves which have not been permanently damaged will regain their function without undergoing degeneration. The recovery curve will then show an initial steep rise, as in the case of traumatic neuritis just cited. Further return of function will depend on the speed at which the damaged nerve fibers regenerate. Factors influencing this are the type of injury, its location and the nerve involved. As a rule, several weeks elapse during which no apparent progress results, as represented by the flat portion of the curve in figure 3.

In order to understand disorders of motor function, other types of study should be used in conjunction with the method described here and the results correlated. Spontaneous activity of single muscle fibers can be recorded with con-

lowing facts: The latent period was commonly three to five seconds, and only occasionally twenty to thirty seconds. Petit mal reactions were observed with application of currents of from 350 to 675 milliamperes for three-tenths second. Their frequency was nearly the same with currents of from 350 to 450 milliamperes, 450 to 500 milliamperes and 500 to 550 milliamperes, and was notably less with currents of from 550 to 600 milliamperes. Severe and moderate convulsions were observed with a current of 300 to 600 milliamperes. However, with higher currents the frequency of severe convulsions greatly increased. With a current of 600 milliamperes given for three-tenths second the convulsions were severe in the large majority of treatments in the same and in different patients.

In some of the patients the reactions to the electric currents were unusual: One patient reacted to 550 milliamperes given for five-tenths second with the usual convulsion. He appeared relaxed for a minute or so; then he had another convulsion, though less severe and of shorter duration. With another patient the duration of the convulsion was remarkably long, namely, fifteen minutes with 500 milliamperes, three minutes with 600 milliamperes and six minutes with 300 milliamperes. One of our patients during the first three treatments reacted with jacksonian-like convulsions: After a latent period for about twenty-five seconds, the patient slowly turned his head to the left; his eyes and tongue deviated also to the left; then the fingers of both hands began to twitch; this was immediately followed by convulsive movements of the right side of the body and by a few clonic movements on the left side. After the convulsion there was a noticeable diminution in the muscular tonus on the left side as compared with that on the right side. In 1 patient a convulsion of fifty seconds' duration in the fourth treatment was followed by apnea for six minutes. With administration of nikethamide and artificial respiration regular breathing was reestablished.

Postconvulsive Reactions.—Nausea with or without vomiting was experienced by a few patients. Fear of the treatment was noted occasionally. One patient after the fifth treatment complained of being afraid of the treatments. Headache, from which he suffered after the preceding two treatments, may have been one of the reasons for his fear. Another patient, after a petit mal seizure, bade those around him good-by and said that he expected to die soon. Five minutes later he reacted with a convulsion to an increased dose; when he came out of the seizure, he complained of headache and expressed the belief that he was already dead. One of us (S.K.) and

associates[1] had previously observed a similar reaction in a patient during metrazol treatment.

Complications. — Complications occurred in only a few of our 276 patients. Three had fractures of the head of the humerus. In 1 of them the fracture occurred during the third treatment. The patient felt greatly improved and was content to have his shoulder broken rather than to suffer the depression. Five patients had vertebral fractures. Curare was given prior to the treatment of 17 patients. One patient had fracture of the femur at the site of a former fracture; the first fracture had been followed by a severe depression.

THERAPEUTIC RESULTS

The therapeutic results obtained in 276 patients are summarized in table 1.

The relatively large number of patients in the schizophrenic group is due in part to the fact

TABLE 1.—*Results of Electric Shock Therapy of Two Hundred and Seventy-Six Patients*

Diagnosis	Number of Patients	Patients Recovered	Patients Showing Improvement	Patients Showing No Improvement
Dementia precox (schizophrenia)	167	43	55	69
Manic-depressive psychosis, depressive type	60	32	16	12
Involutional psychosis (melancholia)	21	6	11	4
Undifferentiated psychoses (schizophrenic-affective features)	19	9	4	6
Psychoneurosis	9	0	5	4

that it includes schizophrenic patients with prominent affective reactions—depression, tension and agitation—and with behavior and feeding problems. On the other hand, we were interested in trying out the treatment on schizophrenic patients without pronounced affective disturbance. Patients with essentially or prominently depressive reactions were included with the patients suffering from manic-depressive, involutional and undifferentiated psychoses, and a number of them, as just mentioned, were placed in the schizophrenic group. The relatively high rate of "recovery" and "improvement" among the last-mentioned patients is to be accounted for, largely, by the therapeutic results obtained in schizophrenic patients with depressive features. However, apparent "recovery" or "improvement" was obtained, also, in patients with fully

1. Katzenelbogen, S.; Brody, M. W.; Hayman, M., and Margolin, E.: Metrazol Convulsions in Man, Am. J. Psychiat. 95:1343, 1939.

ELECTRIC SHOCK THERAPY

CLINICAL, BIOCHEMICAL AND MORPHOLOGIC STUDIES

S. KATZENELBOGEN, M.D.; A. K. BAUR, M.D., AND A. R. M. COYNE, M.D.

WASHINGTON, D. C.

The purpose of this communication is to summarize our clinical observations and to describe more comprehensively studies of the blood and urine made immediately before treatments and at short intervals after convulsions.

CLINICAL OBSERVATIONS

Tolerance.—The following observations on the threshold for convulsions appear to be noteworthy: With 1 patient, three attempts made at five minute intervals to induce a convulsion by application of a current of 450, 500 and 550 milliamperes respectively for three-tenths second in the first treatment and two attempts by application of a current of 500 and 550 milliamperes for five-tenths second in the second treatment were followed by momentary loss of consciousness; five minutes later 600 milliamperes given for five-tenths second caused a severe convulsion, which lasted forty-five seconds. In the third treatment 650 and 675 milliamperes, again given at an interval of five minutes, induced only momentary loss of consciousness. In the fourth treatment 625 milliamperes given for five-tenths second induced a severe convulsion of forty-five seconds' duration. In the fifth and sixth treatments application of 600 milliamperes for five-tenths second also caused severe convulsions of fifty and forty seconds' duration respectively. In another patient 500 and 600 milliamperes given for three-tenths second evoked convulsions. In the third treatment four attempts with application of 600 milliamperes for three-tenths second were followed by four petit mal attacks. In the fourth treatment 600 milliamperes given for three-tenths second again caused a petit mal reaction; five minutes later only 300 milliamperes, but applied for five-tenths second, induced a major convulsion. In a third patient 450 milliamperes, given in two treatments for three-tenths and five-tenths second respectively, caused well pronounced convulsions; then two

successive treatments with 450 milliamperes each, one treatment with 500 milliamperes and another with 550 milliamperes, each given for three-tenths second, were followed by petit mal attacks. Because the patient complained of nausea, no further attempt was made to induce a convulsion. In a fourth patient, in the first treatment, three attempts with 350 milliamperes and two attempts with 450 milliamperes, given for three-tenths and for five-tenths second respectively at intervals of five minutes, caused petit mal reactions. In the second treatment three attempts with 450, 550 and 600 milliamperes respectively for five-tenths second also produced only petit mal seizures; the fourth trial, with 600 milliamperes for five-tenths second, caused a fully developed convulsion of fifty seconds' duration. In a fifth patient 300 milliamperes given for three-tenths second produced a petit mal reaction. Then, three treatments with 350 milliamperes each for three-tenths second were followed by convulsions. In the fourth treatment three applications of 350, 400 and 450 milliamperes respectively for three-tenths second caused only petit mal attack, but in the fourth trial 450 milliamperes for three-tenths second produced a convulsion of sixty seconds' duration.

These cases illustrate our common observation that the patient's tolerance of the electric current may change at intervals of a few days or a few minutes. The tolerance may remain consistently high, though undergoing changes; it also may diminish considerably within a few minutes. To one of us (C.) atmospheric conditions had appeared to have a bearing on the dosage; on a dry, clear day a higher current was required than on a humid day. On the other hand, we also observed notable changes in the tolerance of the electric current in the same patient within a few minutes when atmospheric conditions appeared to be the same. Both change and consistency in the threshold for convulsions were observed with nearly equal frequencies throughout the treatments.

Reactions to the Electric Current.—A survey of the immediate reactions of our patients to the passage of the electric current revealed the fol-

therapy, it should be borne in mind that the deficiency of oxygen in the blood is limited to a short period of apnea during the tonic phase of the convulsions, and that in other phases there is hyperpnea, with corresponding increase of oxygen and decrease of carbon dioxide. But after the convulsion (especially within twenty minutes) in both metrazol and electric shock therapy, there is almost consistently an increase in the oxygen and reducing substances and a decrease in the carbon dioxide in the blood. Thus, if the therapeutic results in convulsive therapy are to be ascribed specifically to changes

laboratory evidences of disturbance in the function of the vegetative organs and the metabolic changes. Thus, both clinical and laboratory observations are indicative of profound disturbances in the physiologic function of the person, in the vital organs and in the metabolism, which disturbances show a definite trend toward hyperactivity. Similar reactions of the person, of the organs and of the general metabolism are prominent in nonspecific protein therapy. It is not far fetched to postulate that the mode of action, namely, activation of the function of organs, attributed with good reason, I believe, to the

TABLE 3.—*Chemical Constituents of the Blood Which Showed Changes After Electrically Induced Convulsions* *

		Treatments			
		Total No.	Increase	Decrease	No Change
Amino acids		50	16 (0.48 to 1.52 mg./100 cc.)	34 (0.19 to 3.19 mg./100 cc.)	..
Icteric index		19	9 (1.7 to 3 3 units)	..	10
Cholesterol		83	60 (8.2 to 91.2 mg./100 cc.)	23 (5.0 to 60.6 mg./100 cc.)	..
Vitamin C		74	57 (0.15 to 0.68 mg./100 cc.)	15 (0.1 to 0.23 mg./100 cc.)	2
Reducing substances		67	60 (11.0 to 72.3 mg./100 cc.)	2 (12.1 to 23.4 mg./100 cc.)	5
Oxygen		68	50 (4.13 to 12.28 vol. %)	16 (3.54 to 12.64 vol. %)	2
Carbon dioxide		67	3 (2.13 to 6.22 vol. %)	64 (5.29 to 33.68 vol. %)	..
Total phosphorus	Serum	19	15 (1.0 to 5.8 mg./100 cc.)	1 (0.3 to 12.1 mg./100 cc.)	3
	Cells	21	12 (0.8 to 6.8 mg./100 cc.)	8 (0.7 to 4.9 mg./100 cc.)	1
Organic phosphorus	Serum	18	12 (0.4 to 5.0 mg./100 cc.)	6 (0.2 to 9.0 mg./100 cc.)	..
	Cells	19	5 (0.4 to 11.6 mg./100 cc.)	14 (0.3 to 12.5 mg./100 cc.)	..
Acid-soluble phosphorus	Serum	20	16 (0.1 to 4.4 mg./100 cc.)	3 (0.1 to 2.8 mg./100 cc.)	1
	Cells	24	10 (0.6 to 3.0 mg./100 cc.)	13 (1.3 to 5.5 mg./100 cc.)	1
Inorganic phosphorus	Serum	52	45 (0.5 to 2.9 mg./100 cc.)	6 (0.1 to 1.3 mg./100 cc.)	1
	Cells	54	48 (1.2 to 8.3 mg./100 cc.)	6 (0.2 to 1.1 mg./100 cc.)	..
Chlorides	Serum	35	21 (5.7 to 19.9 mg./100 cc.)	12 (1.4 to 10.7 mg./100 cc.)	2
	Cells	36	34 (8.5 to 49.0 mg./100 cc.)	..	2
Sodium	Serum	92	67 (5.5 to 20.6 mg./100 cc.)	25 (3.2 to 27.6 mg./100 cc.)	..
	Cells	27	27 (4.2 to 25.6 mg./100 cc.)	..	..
Potassium	Serum	87	56 (5.7 to 22.8 mg./100 cc.)	30 (1.1 to 12.19 mg./100 cc.)	1
Magnesium	Serum	28	20 (0.2 to 1.2 mg./100 cc.)	8 (0.1 to 0.5 mg./100 cc.)	..
Calcium	Serum	41	27 (0.2 to 1.7 mg./100 cc.)	13 (0.1 to 1.1 mg./100 cc.)	1

* These changes were determined within eighty-six minutes after the convulsion.

in the oxidative processes, it would seem appropriate to speak of hyperoxemia rather than of anoxemia.

In trying to understand the mode of action of shock therapies on the physiologic level, one should be cognizant of the fact that change in oxidative processes is not the only effect. Other metabolic alterations take place at the same time, as shown by previous morphologic and chemical studies [5] and by the present investigation. Prominent in the shock therapies considered in this study are the clinical reactions, the

nonspecific protein therapies [5] is equally applicable to the nonspecific shock therapies. But it should be added that the physiologic aspect is not alone to be considered. Multiple psychotherapeutic factors enter into the drama of any of the shock therapies, and contribute their share to the outcome.

5904 Connecticut Avenue, Chevy Chase, Md.
St. Elizabeths Hospital, Washington, D. C.
St. Elizabeths Hospital, Washington, D. C.

5. Katzenelbogen, S.: A Critical Appraisal of the "Shock Therapies" in the Major Psychoses and Psychoneuroses, Psychiatry 2:493, 1939; 3:211 and 409, 1940; La proteinotherapie, Rev. méd. de la Suisse Rom. 42: 5100, 1922.

of the Brain During Insulin and Metrazol Treatment of Schizophrenia, J. A. M. A. 112:1572 (April 22) 1939.

developed schizophrenia, chiefly in the acute phase of their illness. Relapses among schizophrenic patients with depression were much more frequent than among essentially depressed patients. It is noteworthy that in some patients with a condition diagnosed as manic-depressive depression the treatment was followed by lifting of the depressive features and, as it were, by bringing to the fore of the schizophrenic reactions. It appears as though the latent schizophrenic condition was covered by the depression.

Of the patients who were difficult to manage, those with suicidal or homicidal tendencies and those dependent on tube feeding, the treatment was helpful to some, not only in ameliorating their behavior, but in leading to "recovery" and "improvement." Thus, of 28 of such patients, 12 "recovered" and 7 showed "improvement." [2] Some catatonic patients came out of their mutism and behaved as though recovered after only three treatments.

It is interesting to note that in general our patients showed improvement more frequently than not after only three or four treatments.

BIOCHEMICAL AND MORPHOLOGIC STUDIES

Specimens of urine and of blood from the arm vein were obtained before and after treatment from the patients, who were given no breakfast.

Urine.—The acid reaction of the urine remained unchanged after treatment in 38 of 45 instances. In 1 instance the reaction turned from neutral to acid after treatment; in 3 instances, from alkaline to acid, and in 3 instances, from acid to alkaline. In 46 instances the specific gravity showed significant changes after treatment. In 45 instances the reaction for sugar was negative within one hour and forty-five minutes after treatment. There was a trace of sugar before and none within one hour after treatment in 2 instances. In 43 instances the reaction for albumin was negative within one hour after treatment; there was a trace after treatment in 4 instances and a 2 plus reaction after treatment in 6 instances. Microscopic examination revealed nothing abnormal.

Blood.—The methods of analyses used in this study have been described in the articles cited.[3]

Changes in the constituents of the blood following convulsions are summarized in tables 2 and 3.

Both the cellular and the chemical constituents of the blood (amino acids, cholesterol, vitamin C, reducing substances, oxygen, total phosphorus, organic phosphorus, acid-soluble phosphorus, inorganic phosphorus, chlorides, sodium, potassium, calcium and magnesium), as well as

TABLE 2.—*Sedimentation Rate and Morphologic Constituents of the Blood Which Showed Changes After Electrically Induced Convulsions* *

	Treatments			
	Total No.	Increase	Decrease	No Change
Red cells	41	27 (90,000 to 1,770,000)	13 (70,000 to 1,850,000)	1
White cells	41	25 (100 to 5,500)	16 (30 to 2,650)	..
Segmented neutrophils	31	14 (6 to 24%)	15 (4 to 24%)	2
Lymphocytes	29	14 (5 to 24%)	13 (6 to 20%)	2
Monocytes	26	15 (2 to 4%)	6 (1 to 4%)	5
Eosinophils	31	3 (1%)	5 (1%)	23
Sedimentation rate	33	20 (4 to 8 mm.)	12 (1 to 12 mm.)	1

* These changes appeared within one hour after convulsion.

the icteric index, showed changes after treatment; increases often being more frequent than decreases, except for the amino acids, which showed a decrease more than twice as frequently as an increase, and carbon dioxide, which was decreased after nearly all treatments.

COMMENT

Changes in many treatments were not great enough to be important in themselves; yet they gave significance to the more conspicuous alterations in that they emphasized a definite trend. Of the chemical constituents of the blood which undergo changes in the already old-fashioned insulin and metrazol therapies, the reducing substances, oxygen and carbon dioxide have been singled out as the most significant. The therapeutic effects of both these treatments have been attributed to anoxemia, induced by hypoglycemia in insulin therapy and, presumably, by lack of oxygen in metrazol therapy.[4] In convulsive

2. Baur, A. E., and Perrin, J.: Clinical Observations with Electroshock Therapy, Dis. Nerv. System. **5**:180, 1944.

3. Hawk, P. B., and Bergeim, O.: Practical Physiological Chemistry, ed. 11, Philadelphia, P. Blakiston's Son & Co., 1937. Myers, V. C.: Folin-Wu Method, in Practical Chemical Analysis of Blood, St. Louis, C. V. Mosby Company, 1924. Pijoan, M., and Walter, C. W.: A Micromethod for the Determination of Blood Cholesterol, J. Lab. & Clin. Med. **22**:968, 1937. Bessey, O. A.: Vitamin C: Methods of Assay and Dietary

Sources, J. A. M. A. **111**:1290 (Oct. 1) 1938. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry: II. Methods, Baltimore, Williams & Wilkins Company, 1932. Fiske, C. H., and Subbarow, Y.: Colorimetric Determination of Phosphorus, J. Biol. Chem. **66**:375, 1925. Snyder, R., and Katzenelbogen, S.: The Distribution of Sodium, Potassium, Calcium, Magnesium, Inorganic Phosphorus, and Chlorides Between the Blood Serum and Cells of Normal Individuals, ibid. **143**:223, 1942.

4. Himwich, H. E., and Fazekas, T. F.: The Effect of Hypoglycemia on the Metabolism of the Brain, Endocrinology **21**:800, 1937. Himwich, H. E.; Bowman, K. M.; Wortis, J., and Fazekas, J. F.: Metabolism

toms. There was no evidence of the presence of angioma of the retina on examination.

CASE 4.—H. S. B., aged 19, a veteran of World War II, was admitted for treatment of a cerebellar tumor. He had been in good health until January 1941, when he began to experience continuous occipital headaches, which were intensified by his rising from a horizontal position, by lifting weights, by bowel movements and by jarring of the body. Nausea and episodes of nonprojectile vomiting of liquids and solids were manifested later. Visual disturbances, affecting the right eye more than the left, were common. At no time did the patient suffer from spells of unconsciousness or weakness of the extremities. He was admitted to the veterans hospital on May 5, 1944. Neurologic examination revealed the presence of bilateral papilledema, definite coarse nystagmus, with the quick component to the left, and ataxia involving his extremities. The deep reflexes of the upper and lower extremities were diminished. No pathologic reflexes were present. Examination of the spinal fluid and roentgenograms of the skull gave no evidence of any abnormality. The diagnosis was cerebellar tumor, probably hemangioblastoma because of the family history. A bilateral suboccipital craniotomy was performed on June 13, with intratracheal anesthesia. The dura over the cerebellar hemispheres was noted to be under greatly increased intracranial pressure, and removal of the tumor was impossible. The patient died six hours after operation. Autopsy, for verification of the type of tumor and the presence of angiomatous cysts in the retina or other parts of the body, was not permitted.

SUMMARY AND CONCLUSIONS

Tumors of the brain occurred in 4 members of one family—the father, aged 45; a daughter, aged 24, and 2 sons, aged 23 and 19. In 2 members of the family the lesion was a cerebellar hemangioblastoma; in the other 2 members the type of the neoplasm was not determined, but a cerebellar tumor, which could not be removed, was present in 1 of them. Examination of the retina did not reveal the presence of a coexisting angioma. Three of the 4 members of the family died of the cerebral tumor; the other member, a son aged 23, is living and well, after surgical intervention. Since no autopsy was performed, the presence of angiomatous cysts in other parts of the body could not definitely be ruled out. It is probable that the members of this family had Lindau's disease. One sister in the family is well and has not been afflicted with this condition. She is fully aware of the occurrence of tumor of the brain in her family and has sought neurologic examination from time to time as a precautionary measure.

3145 North Cambridge Avenue, Chicago.

Clinical, Technical and Occasional Notes

HANDY AND INEXPENSIVE TEMPERATURE TESTER

THOMAS EDWIN BAMFORD JR., M.D., NEW YORK

Examination of heat and cold sensibility is often neglected during a routine neurologic examination because the tubes used for this test are bulky and unhandy. The tubes on the market for this purpose are also expensive.

container for hypodermic syringe and needle, will serve the purpose well. It is inexpensive (costing 50 cents) and handy, and can be chilled or heated to the desired temperature. It is 15.5 cm. long and 4.5 cm. in circumference at the open end and tapers to a point. As
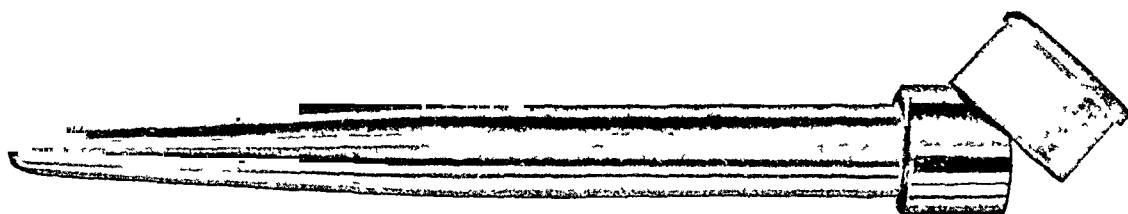
Tube, with rubber cap.

By accident, it was discovered that the tube illustrated here,[1] which has been placed on the market as a sterile

it is plated and smooth, it does not radiate. This tube can be carried in a small container, and the rubber cap affords a firm grip at any temperature.

572 Park Avenue.

---

1. Steritube, manufactured by Becton, Dickinson & Company, Rutherford, N. J.

Case Reports

FAMILIAL INCIDENCE OF TUMORS OF THE BRAIN
Cerebellar Hemangioblastoma

CAPTAIN MAURICE O. GROSSMAN AND MAJOR BENJAMIN H. KESERT
MEDICAL CORPS, ARMY OF THE UNITED STATES

Many papers have been written concerning heredity as a factor in the development of tumors in the human body. Blank,[1] in 1941, reviewed the role of genetics in cancer research. Recently, we had occasion to treat the fourth member of a family to have a tumor of the brain. The occurrence of tumor of the brain in 4 members of one family strongly suggests a familial tendency in certain types of cerebral neoplasms. The predominating type of tumor identified in our cases was hemangioblastoma of the cerebellum. Cushing and Bailey,[2] in 1928, described at length many cases of this tumor. These growths were classified as simple cyst or gliomatous cyst until portions were removed for microscopic examination and a diagnosis of hemangioblastoma was made. The neoplasm occurs almost exclusively in the cerebellum, is usually cystic and has a familial tendency (Sargent and Greenfield [3]). Characteristically, but not always, the tumor is associated with angiomatosis of the retina, or von Hippel's disease.[4] Lindau,[5] in 1926, discovered that this lesion was frequently associated with angioma of the retina and cystic anomalies in other organs of the body. Gross examination may not reveal its presence, but necropsy may show small angiomatous nodules in the spinal cord, kidneys and adrenals, as well as hypernephroma and cysts or angiomas of the liver.

REPORT OF CASES

We present the cases of 4 members of one family with tumors of the brain. In 2 members—the father, aged 45, and a son, aged 23—tumors removed surgically were identified as true cerebellar hemangioblastomas. In the other 2 members, unfortunately, the type of the tumor was not verified. A daughter, aged 24, was

1. Blank, F.: The Role of Genetics in Cancer Research, Ohio State M. J. **37**:947, 1941.

2. Cushing, H., and Bailey, P.: Tumors Arising from the Blood Vessels of the Brain: Angiomatous Malformations and Hemangioblastomas, Springfield, Ill., Charles C Thomas, Publisher, 1928.

3. Sargent, P., and Greenfield, J. G.: Haemangiomatous Cysts of the Cerebellum, Brit. J. Surg. **17**:84, 1929.

4. von Hippel, E.: Vorstellung eines Patienten mit einem sehr ungewöhnlichen Netzhaut, Ber. u. d. Versamml. d. ophth. Gesellsch. **24**:269, 1895.

5. Lindau, A.: Studien über Kleinhirnsystem: Bau, Pathogenese und Beizehungen zur Angiometons retinae, Acta path. et microbiol. Scandinav., 1926, supp. 1, p. 1.

thought to have died of a tumor of the brain, but operation was not completed.

The youngest son, aged 19, was the only member of the family who received treatment at this hospital. On the basis of the history previously obtained, that of the occurrence of cerebellar hemangioblastoma in 2 other members of the family, and of the neurologic signs, a diagnosis of cerebellar tumor, probably a hemangioblastoma, was made. Because of the poor condition of the patient and the tenseness of the dura in the posterior fossa, no attempt was made to remove the tumor. The patient died six hours after operation; permission for autopsy was not granted. Though the presence of a tumor was not verified. the neurologic signs and the presence of bilateral papilledema, with increased intracranial pressure, made likely the diagnosis of a cerebellar tumor. Careful examination of the retina revealed no angiomatous growth. The case records of the other 3 affected members of the family did not reveal the presence of angiomatous growths in any portion of the body. Since necropsy was not performed on any of the 3 patients who died, the presence of small angiomatous growths elsewhere in the body could not definitely be ruled out. Although we have no definite proof that members of this family all had Lindau's disease (combined hemangioma of the cerebellum and the retina), many features of the family history and of the neurologic findings speak for this condition.

Adequate information was obtained concerning the histories of the 3 members of the family who were treated elsewhere. These cases, and the case of the fourth member, are reported briefly.

CASE 1.—The father, aged 45, was first examined in August 1937, when a diagnosis of tumor of the cerebellum was made. On August 26 the presence of a tumor of the brain was verified at operation. A large cerebellar cyst and an associated tumor nodule, 1.5 cm. in diameter, were removed. Microscopic studies proved that the growth was a hemangioblastoma. The patient rallied for two days after operation; then sudden circulatory collapse developed, and he died within ten minutes. It was the opinion of the physician that death was due to coronary occlusion. There was no evidence of involvement of the retina. Autopsy was not performed.

CASE 2.—A daughter, aged 24, had died of a lesion which was probably a cerebellar tumor. Operation was not performed because the patient died suddenly. Autopsy was not performed.

CASE 3.—A son, aged 23, was examined at the University of Oklahoma Hospital in September 1943. Neurologic examination indicated a cerebellar tumor, and there was evidence of increased intracranial pressure. A tumor similar to that of the father was successfully removed. Microscopic studies revealed a hemangioblastoma. Convalescence was stormy, but the patient eventually recovered and is now without symp-

expression and control and in the sense of physical well-being constitutes a diagnostic triad which occurs more frequently than any single neurologic sign. They believe that the affective disturbances in mood and behavior fit in with the patient's previous personality makeup.   CHODOFF, Langley Field, Va.

WORK AND THE PLEASURE PRINCIPLE. IVES HENDRICK, Psychoanalyt. Quart. **12**:311, 1943.

Hendrick formulates the theory that work pleasure is not primarily displaced or sublimated sensual pleasure, but that it is the pleasure afforded by effective integration of the neuromuscular and intellectual functions. He calls the need of human beings for such pleasure the work principle, and he regards this principle as an expression of the instinct to master, the goal of which is control or alteration of environmental situations through the effective development of integrated intellectual and motor functions. The first objective evidence of the work principle is to be observed in the development of each partial function in infancy, when the stereotyped repetition of the function is replaced by the ability to modify the function effectively and to adapt it to tasks which satisfy the need to master. The work principle should therefore be regarded as evidence of maturity of ego function, and the repetition compulsion, as evidence that the ego is functioning inadequately for the skilful performance of a certain task.

PEARSON, Philadelphia.

CONCERNING THE PSYCHOGENESIS OF CONVULSIVE DISORDERS. LEO H. BARTEMEIER, Psychoanalyt. Quart. **12**:330, 1943.

Bartemeier believes that convulsions constitute a means of discharging destructive energy autoplastically. While all human beings have this innate preformed possibility of discharge, the predisposition of those who finally manifest a convulsive tendency consists in their predilection for the convulsive way of discharge. If the energy quantum is high enough and other ways are blocked, even the nonpredisposed person will turn to convulsions in order to relieve the mental apparatus of tension, and to a minor degree every person will show convulsive manifestations in one way or another.

PEARSON, Philadelphia.

FEAR OF DEATH. GREGORY ZILBOORG, Psychoanalyt. Quart. **12**:465, 1943.

Morale has to do with the avoidance of turning aggression against one's self and with the proper direction of aggression outward. The fundamental psychologic issue involved in the problem of morale is that of how one reacts to the fear of death, which is present constantly in mental functioning. It must be kept repressed, and in order to increase the repression one spends much time and energy in denying the possibility of death and in trying to master it. One's interest in news of violent deaths overlays an unconscious egocentricity. "It is not I who was killed."

When war comes to a civilized community, the fear of death, so well taken care of in peacetime, undergoes a crucial change. The civilian may still utilize the mechanism which makes him feel he is an exception and therefore cannot be killed. Not until members of his family and friends fall in battle does he come to grips with the fear of death by way of identification with those who were killed. Therefore compassion, an expression of the unconscious sense of guilt about those who have fallen, and scorn, a momentary sense

of anger and hatred for the enemy who kills, become prominent components of the complex set of psychologic factors that group themselves around the repressed fear of death. Compassion and scorn become the core of morale, and the actual fear of death is mastered through hatred of the enemy. In the civilian who is exposed to bombing the fear of death is activated, but is countered by an increase in religious feeling and the mobilization of hatred. In this way the fear of death is transformed into a sadomasochistic combination, which on the socialized level is represented by awareness of grim hatred and of readiness to make great sacrifices to win the war. The accentuation of murderous drives is helpful in war, but if it occurred in times of peace it would lead to depressive states and to an increase in the rate of suicide. The rate of suicide is always higher in peacetime.

On the battlefield green troops become seasoned soldiers as they become angry, that is, as they convert their fear of death and hatred into hatred and aggression. In that fear of death which would be called neurotic, i. e., in the war neuroses, the victim hates, but he has a paralysis of motor aggression. He is unable to fight because he identifies himself with the dead as a result of a severe sense of guilt which antedates his military service. Those who are the most conspicuous misfits on the battlefront are the most ethically sensitive people, although they are socially the most useless.

Civilian morale might be improved if the general population were better informed about the losses and could see more of the wounded.

PEARSON, Philadelphia.

BODY AS PHALLUS: A CLINICO-ETYMOLOGICAL NOTE. HENRY ALDEN BUNKER, Psychoanalyt. Quart. **12**:476, 1943.

The English word "body" is of unknown origin. Middle Gaelic, however, has the word bod, meaning penis. This corresponds to the psychoanalytic observation that body and penis are interchangeable in the unconscious. Bunker cites the fantasy of a 6 year old boy, which illustrates clearly that for this boy the word "body" meant penis.   PEARSON, Philadelphia.

THE PSYCHOANALYTIC CONCEPT OF MEMORY AND ITS RELATION TO RECENT MEMORY THEORIES. ERNST LEWY and DAVID RAPAPORT, Psychoanalyt. Quart. **13**:16, 1944.

The psychoanalytic theory of memory is based on the view that memory traces are used by psychic forces, which find expression through them. The modes in which strivings make use of memory material vary significantly among such phenomena as everyday remembering, dreams and remembering of childhood experiences. The theories of memory deduced from experimental work by Lewin, Koffka and Bartlett show a striking parallel with the psychoanalytic theory.

PEARSON, Philadelphia.

HYPOGLYCEMIA AND TENSION-DEPRESSION. T. A. C. RENNIE and J. E. HOWARD, Psychosom. Med. **4**: 273 (July) 1942.

Rennie and Howard report on a series of 7 patients who had symptoms of a psychiatric disorder characterized chiefly by tension and colored by manifestations of depression. In addition, all the patients exhibited, as a conspicuous feature, a craving for food, which when satisfied resulted in temporary alleviation of the

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

___

Psychiatry and Psychopathology

LATE EFFECTS OF LEAD POISONING ON MENTAL DE-
VELOPMENT. R. K. BYERS and E. E. LORD, Am. J.
Dis. Child. 66:471 (Nov.) 1943.

According to Byers and Lord, it has not been gen-
erally recognized that lead poisoning occurring in early
life usually has a disastrous effect on mental develop-
ment. They present a follow-up study of 20 school
children who had been hospitalized in infancy or early
childhood because of lead poisoning. None of them
exhibited striking evidence of encephalopathy during
their primary admission, and all were adjudged to
have made a complete recovery from lead poisoning
when discharged from the original hospitalization. The
authors emphasize the length of the cycle of ingestion,
the storage and elimination of lead in relation to the
relatively short duration of the symptoms and the signs
allowing a diagnosis of lead poisoning. It is probable
that lead poisoning of the sort discussed here can at
present be recognized in only a small percentage of
cases. Failure of the normal processes of growth and
development of the cortex prevented all but 1 of the
20 children from progressing satisfactorily at school.
In addition to difficulties in the general intellectual and
sensorimotor spheres, other evidence of interference with
the normal development of the nervous system was
present. Recurrent convulsions appeared in 3 of the
children, at 4, 4½ and 5½ years of age respectively.
One girl who had peripheral neuritis as a baby acquired
a positive Babinski sign, and a boy who was discharged
from the hospital as well at about 3 years of age had
hyperactive reflexes and sustained clonus of the left
ankle when reexamined at 9 years of age. Behavior
difficulties were common throughout the series. Much
of this behavior could be classified as "forced reaction
to stimuli in the environment," described by Strauss and
Werner as an evidence of cortical damage. It was
apparently the result of loss of the normal inhibitory
function, thought to reside in the cortex. It was
usually described as unreliable impulsive behavior, cruel
impulsive behavior, short attention span and the like.

J. A. M. A.

___

ALTERATIONS IN COMMUNICABILITY, CONTENT OF
THOUGHT, AND AFFECTIVE RESPONSE DURING IRRI-
TATIVE (CAMPHOR) THERAPY. EMERICK FRIEDMAN,
J. Nerv. & Ment. Dis. 98:229 (Sept.) 1943.

Friedman studied the alterations in the productivity
of 70 previously noncommunicative psychotic patients
who were given camphor therapy. In the preparatory
phase, the selection of a group of patients, their segre-
gation from others and the excitement of the treatment
fostered an *esprit de corps* among them which resulted
in a banding together, but did not change the nature of
their thought content. The injection of camphor in-
duced irritative delirium with a feeling of impending
annihilation. In practically every patient, even those
with a previously acute psychosis, there was produced
a verbal response communicating the necessity for
haste and quick preventive action. At first symbolic
implements were used, but with succeeding treatments
an increasingly direct and understandable speech was
employed. Many of the patients began to write letters
for the first time since institutionalization. Disturbances
in equilibration were noted frequently, in the nature of
experiences of rapid alterations of equilibrium. These
were accompanied by terrifying feelings of disorganiza-
tion. Somatic complaints usually centered about the
thorax and abdomen, while actual skeletal injuries,
such as sprains, or even fractures, were disregarded.
Various motor manifestations of sexual activity were
observed during the delirium. These included mas-
turbatory and heterosexual and homosexual pantomimes.
Several patients revealed vague sadistic or masochistic
trends. Pathologic sexuality was also released verbally.
Almost every patient expressed experiences of body
alterations that might be classified as castration fears.
Even in previously apathetic patients, an affective
appropriateness was called forth, as well as increased
sensitivity and sudden impulsive destructive and self-
destructive outbursts.

The author suggests that these alterations in produc-
tivity and affect could be employed in psychotherapeutic
efforts accompanying the irritative therapy.

CHODOFF, Langley Field, Va.

___

MENTAL SYMPTOMS IN MULTIPLE SCLEROSIS. CARL
SUGAR and RAYMOND NADELL, J. Nerv. & Ment.
Dis. 98:267 (Sept.) 1943.

Sugar and Nadell review the literature on the mental
symptoms of multiple sclerosis, emphasizing the great
diversity of observations by different authors. They
attribute this primarily to the difference in the source
of the material studied, this being exclusively either
from neurologic hospitals or from institutions for mental
disease.

They report a study of 28 patients with multiple
sclerosis admitted to a hospital for chronic neurologic
conditions. They found euphoria to be the prevailing
mood in 15 patients, dysphoria in 5 and fluctuating
moods in 8 patients. As a change from their prevailing
mood prior to the onset of the illness, 11 patients
showed an increase in cheerfulness; 10 of these were
basically cheerful. Seven patients showed an increase
in depression; in 4 this was the prevailing mood. Six
patients showed an increased variability of mood; of
these, all but 1 had always had variable moods. Four
patients displayed no change. Thus, in the majority
of patients the prevailing mood was accentuated. In
all but 2 of the patients the affective coloring of the
thought content was similar to that of the prevailing
mood. A sense of physical well-being accompanied the
mood in the euphoric patients, whereas the dysphoric
patients felt bad most of the time. Exaggerated emo-
tional expression was present in 79 per cent, while 21
per cent of the patients showed little outward expression
of emotion. Loss of or imperfect control of affective
expression was found in 18 patients (64 per cent); 16
of these stated that their outward expression was in-
congruous with their emotional feeling.

The authors corroborate the contention of Cottrell and
Wilson that change in the prevailing mood, in emotional

329

After the neurosis is established, the emergency treatment is as follows: (1) Controlled sleep, physical restoration and friendly group companionship; (2) superficial catharsis through companionship in isolation, "gentling" and opportunity for cathartic release; (3) prolonged sleep under continuous narcosis; (4) group methods of psychotherapy; (5) deconditioning procedures; (6) hyponarcoanalysis and the induced hypnagogic reverie, and (7) in cases in which the patient is inaccessible to any contact, even under narcosis, one or two electric shock treatments or sustained periods of hypoglycemia, without coma or convulsions.

PEARSON, Philadelphia.

PSYCHOSES IN OFFICERS IN WORLD WAR II. ADDISON M. DUVAL, War Med. **5**:1 (Jan.) 1944.

Duval reports on the study of 100 officers admitted consecutively to St. Elizabeths Hospital and compares this group with a somewhat similar group of officer patients in World War I.

Twenty-seven patients gave a history of previous mental illness, and 10 had previously been treated in hospitals for mental disease. At least 20 of the 27 patients would have been rejected on induction if they had been given an adequate psychiatric examination. The ages of the entire group varied from 20 to 49 years. Eleven men had service of less than one month, and 45, of less than one year. In many instances situational factors were important in producing the psychotic attack. Thirty-four patients had manic-depressive psychoses, and 30, schizophrenia. With 10 patients electric shock gave good results. Seventy-four patients have been discharged from the hospital, 49 as recovered or socially recovered, 20 as showing improvement, 2 as showing no improvement and 3 as free from psychosis.

PEARSON, Philadelphia.

HYSTERICAL VISUAL DEFECTS. PAUL T. McALPINE, War Med. **5**:129 (March) 1944.

McAlpine reports briefly 9 cases of amblyopia of hysterical origin and 1 case of amblyopia regarded as a symptom of dementia precox. Hysterical amblyopia is of infrequent occurrence and must be differentiated from retrobulbar neuritis, toxic neuritis and amblyopia due to disease of the central nervous system.

PEARSON, Philadelphia.

RETROGRADE AMNESIA. W. MAYER-GROSS, Lancet **2**: 603 (Nov. 13) 1943.

Mayer-Gross tested retrograde amnesia in 102 trials on 46 patients. The subjects were all psychotic, without impairment of memory; the author excluded patients whose full cooperation was doubtful. Tests were made for memory of a series of four picture cards the minute prior to the administration of electric shock therapy. After twenty-four hours or less the patient was tested for memory recall and for recognition. Only 2 patients recalled all cards, and of all 102 tests only 29 resulted in complete recognition. The author stated that this result indicates that retrograde amnesia is not a universal symptom after epileptiform convulsions. There was a direct relation between the time the pictures were shown and recall and recognition; the pictures shown first were better remembered than those shown next, and the pictures shown last were least often recalled or recognized. Thus the defect was true retrograde amnesia. The results of testing three to eight hours after the shock were compared with those of tests made twenty-four hours later. The first picture shown was

consistently better remembered a few hours after the seizure than a full day later. The author concluded that this observation indicated that "it is not a matter of indifference at which time the patient is tested for retrograde amnesia." In only one tenth of the experiments did the retrograde amnesia last longer than one minute.

Mayer-Gross discusses the theories explaining this phenomenon. The most popular current theory among neurologists and psychiatrists is that the traces, or engrams, of what has gone before the accident are destroyed. The author believes that the difference between recall and recognition in his tests is too great to support this theory by which he means that one could not recognize so well what one could not recall if the subject matter had been actually destroyed or blotted out. Rather, he prefers the theory that the consolidation of recent memories is interrupted; there is a retroactive inhibition similar to that known to normal psychology.

He cannot explain the individual differences in retrograde amnesia found among his subjects. In patients with head injuries the variations might be explained by differences in local cerebral damage, but the duration of electric shock and its clinical symptoms vary so little from subject to subject "that one is forced to surmise the presence of an unknown personal factor." Nor can he explain the clinical fact that patients in post-traumatic drowsiness will describe an accident in detail which they cannot remember when completely conscious later. This phenomenon seems to parallel the fuller recollection of the first picture in the early test of his series.

McCARTER, Philadelphia.

Diseases of the Brain

INCIDENCE OF THE CHANGES IN THE RETINAL VEINS IN MULTIPLE SCLEROSIS. J. V. TRUESCH and C. W. RUCKER, Proc. Staff Meet., Mayo Clin. **19**:253 (May 17) 1944.

Rucker describes perivenous sheathing in the retinal veins in cases of multiple sclerosis and asserted that in most of the cases in which this sign was present a definite or a presumptive diagnosis of multiple sclerosis had been made.

Truesch and Rucker report on the examinations of the fundus in 52 patients with multiple sclerosis, in all of whom careful search was made for perivenous sheathing. All the examinations were made through dilated pupils; all observations were confirmed, and all borderline cases were discarded. Of the 52 patients studied, 10 (19 per cent) showed the changes described as perivenous sheathing. The ages of the 10 patients varied from 18 to 51, 5 being women and 5 men. The average time of appearance of the sheathing after the first symptom of multiple sclerosis was four and one-third years. The condition is not related to the occurrence of pallor of the optic disks nor to a history of previous blurring of vision.

ALPERS, Philadelphia.

LEBER'S DISEASE: REPORT OF FOUR CASES IN ONE FAMILY. C. S. ALEXANDER, Texas State J. Med. **39**:301 (Sept.) 1943.

Leber's disease is defined as hereditary bilateral primary optic nerve atrophy. It is transmitted almost entirely by the female, who is usually unaffected, although it may rarely be transmitted by the male directly or indirectly through the daughters. It may be seen in successive generations, but it usually skips one or

emotional disturbances. Six of the patients were women, and 1 was a man. The hypoglycemic symptoms were in keeping with the flat dextrose tolerance curves obtained for all the patients. The hypoglycemia appeared to be secondary to the psychiatric disorder, since the former disappeared after the treatment of the latter. The authors emphasize that, since there are wide variations in the level of the blood sugar outside the accepted normal range, the dextrose tolerance test should be properly interpreted in terms of the individual personality. They conclude that when the specific complaints suggestive of hypoglycemia are presented, it is important to study the total personality and, in a certain group of patients, to treat the personality disturbances primarily.

SCHLEZINGER, Philadelphia.

PHYSIOLOGIC AND PSYCHOLOGIC STUDIES IN SPONTANEOUS HYPOGLYCEMIA. J. ROMANO and G. P. COON, Psychosom. Med. **4**:283 (July) 1942.

Romano and Coon describe the case of a married man aged 44 in which the original diagnosis of hysterical fugue was later proved incorrect and was replaced by a pathologically verified diagnosis of hypoglycemia due to a benign islet cell adenoma of the pancreas. The patient was an emotional, rigid, sensitive and dependent person who evidenced considerable repressed aggression. His illness was also characterized by recurrent episodes of confusion, uninhibited emotional behavior and disconnected movements. After the surgical removal of the adenoma the episodes were eliminated, but the essential nature of his personality remained unchanged.

The authors believe that the principal source of error in the diagnosis of a neurotic personality lies in the methods directed toward exclusion of positive data related to physical disease or psychosis. The need for the establishment of positive criteria of neurotic personality structure is emphasized.

In considering the relation between increased cerebral metabolism as a result of hypoglycemia and the resultant disturbances in intellectual, emotional and motor behavior, the authors suggest that inhibition and repression may be the physiologic and psychologic expressions of a basic phenomenon. The release of concrete intellectual activity, of less inhibited emotional expression and of less integrated neurologic behavior may result in all delirious patients as it did in this hypoglycemic patient. As in all deliriums, the primary psychologic disturbance is situated at the level of awareness. This disturbance of consciousness is more or less impersonal. On the other hand, the emotional behavior, which is dependent on the degree of disturbance of consciousness, is more individualized and specific in reflecting the personality structure of the delirious patient.

SCHLEZINGER, Philadelphia.

A PERSONALITY STUDY OF ALCOHOL ADDICTION. CHARLES C. HEWITT, Quart. J. Stud. on Alcohol **4**:368 (Dec.) 1943.

Hewitt employed the Minnesota multiphasic personality schedule and the Pressey senior classification test in an effort to determine the personality of persons addicted to alcohol. He claims that the schedule employed appears to be superior to any other inventory. The case material consisted of 37 members of Alcoholics Anonymous, Inc., 15 other persons with alcoholism and 12 subjects who enjoyed the effects of alcohol but rarely drank in excess. The author concludes that addiction to alcohol seems to accompany, with few

exceptions, deep personality disorders. Nearly all of the alcohol addicts, according to this study, exhibited a "marked psychopatic deviation which was often associated with neurotic, paranoid or schizoid trends."

GUTTMAN, New York.

PHYSICAL TREATMENT OF ACUTE PSYCHIATRIC STATES IN WAR. WILLIAM SARGANT, War Med. **4**:577 (Dec.) 1943.

Sargant points out that persons with reasonably good previous personalities do not generally break down or give up the fight against neurotic symptoms if their physical health is good. In treatment of acute conditions he emphasizes the need for sedation, preferably administration of the barbiturates intravenously or of paraldehyde by mouth. Forced feeding of enormous quantities of food and liquids is necessary with patients who have lost weight. This may be supplemented by small doses of insulin or by the Weir Mitchell technic. Sargant ends with the statement "Breakdown, even in the presence of great physical exhaustion and deterioration, is less common in an advancing triumphant army."

PEARSON, Philadelphia.

MANUAL OF EMERGENCY TREATMENT FOR ACUTE WAR NEUROSES. LAWRENCE S. KUBIE, War Med. **4**: 582 (Dec.) 1943.

Most war neuroses begin as acute disorders. These disturbances frequently develop gradually; i. e., the collapse occurs only after cumulative stress. Paramount in this stress are the effects of fatigue and hunger, of incessant and increasing danger and of a series of repeated, rapidly successive, narrow escapes. It takes time to recover from the effects of sudden danger; but when one threat is followed at once by another, there is no interval in which the emotional reverberations can die out, and the person spends his days and nights living as though he were engaged in an incessant struggle to escape from or master the original danger. Each successive escape contributes to the secretly mounting tension. At some point the tension becomes manifest, usually the first sign being a specific disturbance of sleep and terror dreams. Once sleep is disturbed, fatigue increases rapidly, giving rise to moments in the waking hours in which the patient lapses into momentary half-dissociated states. At such moments sudden movements, noises or lights cause a startled panic. As the fatigue and moments of terror spread through the day, the patient becomes unstable and depressed and feels alienated from his comrades. There are also many subtle changes in his daily behavior.

As any man may break under sufficient stress, prevention depends on the recognition of incipient stages and on steps which can be taken to stave them off. There are several important preventive measures: 1. Officers and men should be taught to recognize early any disturbances of sleep. 2. As soon as sleep disturbances are noted, sedation, with a combination of two sedatives, should be given; one of the sedatives should act rapidly, and the other should act slowly and have a sustained action. 3. A low light should be kept burning in the sleeping quarters throughout the night. 4. The soldier should be awakened swiftly and be given a cold drink or black coffee, followed by amphetamine sulfate, as soon as he is awake. 5. Rest periods during the day should not be silent, but the soldier should be kept amused and interested.

ered. Encephalitis associated with exanthems has been attributed to the virus of the exanthem in question; to a virus common to all patients, normally latent, but activated by the exanthem, and to an allergic reaction in the brain following the general eruption. Bradford seems to favor the last theory.

ECHOLS, New Orleans.

HEAD INJURIES IN MOTOR CYCLISTS WITH SPECIAL REFERENCE TO CRASH HELMETS. H. CAIRNS and H. HOLBOURN, Brit. M. J. **1**:591 (May 15) 1943.

Cairns and Holbourn, in an extensive analysis of 106 cases of head injury sustained by motor cyclists wearing crash helmets, noted the following significant observations: The degree of injury varied from mild to severe. The injury of the scalp and skull corresponded with the site of the blow on the helmet. In 40 per cent of 81 cases the victim sustained multiple injuries to the head. Over half the blows occurred on the front of the helmet, and the crown received the least number of blows. The authors noted that in motor cyclists cerebral injury was almost invariably associated with a blow on the head, protection against which could be provided by a properly fitted crash helmet; only rarely was the brain damaged by a blow limited to the face. The wearing of the crash helmet reduced the incidence of fracture of the skull, decreased the degree of concussion and altered the severity of the injury in the direction of mildness. A comparison of the two types of crash helmets revealed the superiority of the pulp over the vulcanized rubber helmet.

ECHOLS, New Orleans.

ARSENICAL ENCEPHALOPATHY. R. B. NELSON, C. McGIBBONS and F. GLYN-HUGHES, Brit. M. J. **1**: 661 (May 29) 1943.

Hemorrhagic encephalopathy is one of the rarest and most fatal complications occurring during the treatment of syphilis with arsenical compounds. The reason for its occurrence is not definitely understood. The dose and toxicity of the drug seem to bear no relation to its production. The authors consider as possible etiologic factors the nature of the syphilitic infection, vitamin deficiency and mental stress and strain. They believe that the drug has a direct toxic action on the cerebral capillaries. They regard pregnant women as "potential reactors." The clinical picture is one of cerebral irritation, which may be preceded by symptoms of headache and dizziness. Four cases are reported, in 3 of which the complication was fatal. In the other case recovery was attributed to repeated spinal drainage and the use of morphine.

ECHOLS, New Orleans.

NEUROHEPATIC DEGENERATION. T. FRACASSI, Rev. argent.-nort. de cien. méd. **1**:310 (July) 1943.

Fracassi shows that, contrary to Wilson's and von Economo's belief, the degenerative process in hepatolenticular degeneration is not limited to the lenticular nuclei and the putamen, but extends to the cerebral cortex, the white substance and the gray nuclei. He states therefore that neurohepatic degeneration would be a better term and includes under it not only Wilson's disease and the pseudosclerosis of Westphal and Strümpell but all cerebral degenerative alterations caused by degenerative hepatic lesions. A case is described in which the condition could be considered Wilson's disease but was really atrophic cirrhosis of Laënnec, prob-

ably due to a gastrointestinal disorder, since alcoholism or syphilis was absent. The patient showed neurologic manifestations ten years after onset of the first symptoms of hepatic cirrhosis. The first neurologic manifestation was mild paralysis of the hands and legs. Later, speech became slow and hesitant, and tremor of the hands developed. Clinical examination revealed an extrapyramidal syndrome, with parkinsonian rigidity of the face and tremor of the hands, moderate muscular rigidity and dysarthria and tremor of the lips and tongue with difficulty in swallowing. There were also signs of a pyramidal syndrome: pronounced decrease in the strength of limbs, exaggerated tendinous reflexes, bilateral clonus of the foot and a positive Babinski sign in the left foot. The patient also presented symptoms of cortical excitation in the form of epileptiform fits. He died of pneumonia, and necropsy showed atrophic cirrhosis of the liver with fibrous perihepatitis and interstitial splenitis, as well as varices of the esophagus. There were atrophy of the cerebral cortex, laminar softening and atrophy of the nuclei of the striatum, with softening and cystic dilatation of the perivascular spaces and areas of softening in the optic layer. Glial elements were abundant in the cortex and in the nuclei of the striatum. There were areas of circumscribed and diffuse loss of nuclei in the frontoparietal white substance.

J. A. M. A.

ACTION OF CARBON DIOXIDE IN EPILEPSY AND SCHIZOPHRENIA ON BASIS OF ELECTROENCEPHALOGRAPHIC OBSERVATIONS. A. F. KORNMÜLLER, München. med. Wchnschr. **89**:30 (Jan. 9) 1942.

Kornmüller investigated the influence of carbon dioxide on the electroencephalographic changes in patients with epilepsy and with dementia precox. The patients were subjected to electroencephalographic study while they breathed alternately ordinary air and 5 or 3 per cent carbon dioxide in pure oxygen. These studies were made on 40 patients, most of whom had either epilepsy or dementia precox. The observations demonstrated that carbon dioxide may decrease or completely counteract the abnormal electroencephalographic manifestations of these diseases. Carbon dioxide, especially its deficiency (hypocapnia), acts directly on the brain, inasmuch as it is an adequate stimulus for certain parts of the brain. Carbon dioxide increases the perfusion of blood in the brain, whereas its lack reduces the cerebral circulation. Carbon dioxide also plays a part in tissue respiration. Further investigations are necessary to determine which of the factors assumes the decisive role. The author's observations indicate that some patients with epilepsy or with dementia precox are more or less continuously, and not during hyperventilation alone, in an abnormal state, which can be counteracted by carbon dioxide. Electroencephalography indicates that this condition involves chiefly parts of the frontal area of the brain which are connected with the midbrain and the hypothalamus. It is possible that these parts of the brain are diseased or that carbon dioxide represents an adequate stimulus for some of them. This is also indicated by the effect of voluntary hyperventilation in patients with epilepsy. It is probable that therapeutic effects may be expected from the use of carbon dioxide in treatment of epilepsy, dementia precox and other diseases of the brain. The effects of metrazol, insulin and electric shock treatments may be partly due to the fact that these methods increase the carbon dioxide content of the brain and blood.

J. A. M. A.

more generations. The disease frequently affects more than one person in a family and involves males more frequently than females. The literature records 1 case in which microscopic examination of the optic nerve was made post mortem, by Rehsteiner in 1932. This author observed atrophy of the ganglion cells and the nerve fiber layer of the retina and atrophy of the optic nerve, limited to the papillomacular bundle, other parts of the nerve being normal. The medullary sheaths were almost all destroyed. There were an increase in the glia and atrophy of the finer connective tissue partitions of the nerve. Alexander observed 4 cases of Leber's disease in a family of 5 children. The cases were equally distributed between the sexes. In the 2 girls the onset of the disease was at 5 years of age, whereas usually the first symptoms occur between puberty and the age of 30 years. In these patients the condition did not improve. One patient presented an associated nystagmus; this is unusual in the presence of greatly reduced vision. No other record of its concurrence with Leber's disease could be found. The chief symptom is great diminution in vision with central scotoma. Complete blindness does not occur. The prognosis is poor, but improvement sometimes occurs. Treatment is of no benefit.

J. A. M. A.

ATMOSPHERIC AND IMMERSION BLAST INJURIES. FRANK V. THEIS, War Med. 4:262 (Sept.) 1943.

Atmospheric and immersion high explosive blasts produce injuries to the internal structures of the exposed body with absence of external evidence of trauma. There may be symptoms referable to all parts of the body. With respect to the nervous system, headaches are common, and sensitivity to noise and tinnitus are fairly frequent. Changes in the personality are important and become most prominent several days after injury.

Relatively few cases of blast injury have been studied adequately at autopsy. The air-containing viscera seem primarily to be injured by blast. Injuries to the kidneys, spleen and liver have not been observed at autopsy, but animal experiments have demonstrated that all organs may be affected.

There is no essential difference between the injuries resulting from atmospheric blasts and those due to immersion blasts. The detonation of high explosives produces an extremely intense longitudinal compression wave, which moves forward, although the particles of the medium through which it passes do not move, but oscillate backward and forward. The wave has two phases—a pressure and a suction component. It travels four times as far in water as in air. The damaging effect of the blast wave is due largely to the sudden pressure of the external surface of the body on the internal structures.

In order to prevent the serious effects of blast on the body, the following protective measures may be taken:

1. In the presence of an impending blast, one should exhale forcibly and contract the abdominal muscles.

2. For atmospheric blasts, protection is afforded by shelters, heavy clothing and cotton or plastic appliances for the ears. It is important to lie face down in a trench or gutter.

3. In the presence of immersion blasts, one should keep the head, and as much of the body as possible, out of the water, by swimming on the back, and should keep the mouth open. It is advisable to wear a heavy kapok life jacket and delay as long as possible entering the water when immersion blasts are expected.

The treatment for blast injuries is symptomatic, and its appropriateness depends on the extent, severity and distribution of the injuries.

PEARSON, Philadelphia.

NIGHT BLINDNESS OF WAR. PAUL H. WOSIKA, War Med. 4:331 (Sept.) 1943.

Malnutrition (lack of vitamin A) causes night blindness, xerosis and xerophthalmia. Therapeutic correction is simple, swift and sure. Although in the literature poor dark adaptation, as measured by instruments, has been included under the term night blindness, it is not related to it, and treatment with huge doses of vitamin A does not correct it.

PEARSON, Philadelphia.

APPLICATION OF ELECTROENCEPHALOGRAPHY IN THE NAVY IN WARTIME. ROBERT S. SCHWAB, War Med. 4:404 (Oct.) 1943.

Ninety per cent of the naval personnel with clinical epilepsy have had abnormal electroencaphalograms. Electroencephalography has proved thoroughly useful in the diagnosis of, or in the elimination of a suspicion of, an epileptic tendency. The electroencephalographic examination, however, is not a short cut, nor does it eliminate the need for a careful history and neurologic study.

PEARSON, Philadelphia.

HYSTERICAL HOMONYMOUS HEMANOPSIA WITH HEMIPLEGIA AND HEMIANESTHESIA. SLOAN G. STEWART, GREG C. RANDALL and F. REGIS RIESENMAN, War Med. 4:606 (Dec.) 1943.

The authors report the case of a man with homonymous hemanopsia associated with hemiplegia. Several examinations of the visual fields showed a constant field defect, consisting of homonymous macula-sparing hemanopsia consistent with a diagnosis of an organic lesion of the brain affecting the right optic pathway or tract. The subjective sensory and motor complaints were compatible with such involvement. The clinical course, the objective neurologic observations and the efficacy of psychotherapy indicated the hysterical condition. A review of the literature indicates that perhaps this is the first case of homonymous hemanopsia of a true hysterical nature ever to be reported.

PEARSON, Philadelphia.

ELECTROENCEPHALOGRAPHY IN THE ARMY GENERAL HOSPITAL. DANIEL SILVERMAN, War Med. 5:163 (March) 1944.

On the basis of the study of the clinical records and electroencephalographic tracings for 173 neuropsychiatric patients, Silverman concludes that the electroencephalogram is of special value in the diagnosis and disposition of epilepsy, psychoneuroses resembling organic disease of the brain, syndrome following head injury and focal lesions of the brain from any cause.

PEARSON, Philadelphia.

TWO CASES OF RUBELLA MENINGO-ENCEPHALITIS. R. I. C. BRADFORD, Brit. M. J. 1:312 (March 13) 1943.

The rarity of meningoencephalitis in association with rubella is evidenced by the fact that Taylor, in 1937, could find only 12 reported cases. Bradford reports a case of such an occurrence in a youth aged 19 years and another in a boy of 18 years. Both patients recov-

Society Transactions

CHICAGO NEUROLOGICAL SOCIETY

R. P. MACKAY, M.D., *President, in the Chair*

Regular Meeting, Feb. 8, 1944

Intracranial Chordoma: Report of a Case. DR. PETER BASSOE.

A single woman aged 32, a private secretary, was seen by me in 1937 because of mild paralysis agitans involving the right side which had come on six years before without any signs of encephalitis or other acute infection. I did not see her again until January 1942, when the paralysis agitans was no worse but she complained of sore eyes. The vision and eyegrounds were normal. In February 1943 she complained for the first time of getting tired and of more difficulty with the right hand. On April 1, 1943 she awoke with severe headache on the left side and triplopia on looking to the left. When she was seen on April 5, the presence of triplopia was verified, and the left rectus muscle was about 30 per cent paretic. The headache was relieved by codeine. On admission to the hospital on April 6, she still had the triplopia but little headache. Examination by Dr. E. V. L. Brown on the day after admission revealed only diplopia. The palsy of the external rectus muscle remained, with the width between the images constantly changing. The pupils and the disks were normal. In a few days the palsy of the external rectus muscle almost disappeared, and the patient saw double only on looking to the far left. She left the hospital on April 10. Aside from the diplopia, the neurologic condition was unchanged. She was in her usual condition,· free from diplopia, until the last week in July, when slight palsy of the left external rectus muscle reappeared, and she also complained of headache in the left frontal region. The weakness of the external rectus muscle slowly increased, to be complete by the end of August. In late September the tongue and the inside of the mouth on the left side became hypalgesic, and in the course of a month the whole area of distribution of the left trigeminal nerve was analgesic. There was much headache, and at night she would wake with twitchings on the right side.

She continued work until she had to give up, chiefly on account of fatigue, and she returned to the Presbyterian Hospital on October 18. Soon speech became slurred and swallowing difficult, and weakness of the right side was added to the old parkinsonian rigidity. The visual fields were practically normal on October 21. The eyegrounds remained normal until about October 28; then papilledema rapidly developed bilaterally. Neither the lateral nor the anteroposterior roentgenogram of the head showed anything abnormal. The pineal shadow was in the midline. Spinal fluid obtained on October 18 was clear and colorless; the pressure was 190 mm.; the Wassermann and Lange reactions were negative, and the cell count was 1 per cubic millimeter. The protein measured 44 mg. and the sugar 68 mg. per hundred cubic centimeters. Chiefly in the hope that the severe headache might be relieved, burr holes were made in both occipital bones by Dr. Verbrugghen, on November 1. Abundant fluid, under increased pressure, was obtained from the right

ventricle, but little came from the left. The protein content of the ventricular fluid was only 8 mg. per hundred cubic centimeters. No air was injected, as by this time my colleagues and I were convinced of the presence of an inoperable tumor on the left side. The relief from headache was complete and permanent, much to our surprise. The patient grew weaker and more stuporous from day to day, and finally fever, leukocytosis and signs of bronchopneumonia developed. She died on December 15. The clinical diagnosis was old, stationary paralysis agitans and a deep-seated cerebral tumor involving the left side of the brain stem. Necropsy revealed a large nodular tumor beneath the pons. It had eroded the bone between the sella and the foramen magnum, including the left posterior clinoid process. The pituitary gland was of normal size and appearance. The brain showed no other gross lesion. Examination of the rest of the body showed nothing of importance except beginning lobular pneumonia.

Histologic examination of the tumor revealed the structure of a typical chordoma. In one microscopic section the three characteristic stages were present: (1) the stage of densely packed cells, mostly without vacuoles, (2) the stage of extensive vacuole formation and (3) the stage of vacuole formation with the addition of syncytial formations. No mitotic figures were seen. As all the material had been placed in a solution of formaldehyde, it was impossible to use a special stain to determine whether the material in the vacuoles was glycogen, which is generally supposed to be present in this tumor. A piece of bone from the eroded basilar process which had been decalcified showed the same tumor structure.

At the time of this report nearly 100 cases of cranial chordoma have been reported, but a positive clinical diagnosis has been possible only by biopsy when the tumor extended into the nasopharynx, an occurrence which is said to have been noted in 20 per cent of cases. However, the diagnosis is almost certain if the roentgenogram reveals a depression in the bone near the spheno-occipital junction and if the ventriculogram shows elevation of the third and fourth ventricles above the base of the skull. The clinical picture is never completely convincing but is often extremely suggestive, and is dominated by progressive involvement of the cranial nerves. The commonest early local symptom is diplopia, due to paresis of the external rectus muscle, preceded or accompanied by localized or general headache. The other cranial nerves most frequently involved are the fifth and the tenth, but all the cranial nerves are subject to involvement, the selection depending on how far forward and backward the bone tumor extends. Penetration of the tumor into the brain is uncommon, and involvement of the cranial nerves is the result of their being stretched by the lifting up of the brain by the tumor at the base. Choked disk is not common and occurs late in the course of the disease. Hemiplegia and other symptoms of cerebral compression, if present, are of late appearance.

Surgical treatment has been tried in several cases, usually with such poor results that we do not regret our failure to attempt it in the present case. Even if the confusing preexisting paralysis agitans had not

Peripheral and Cranial Nerves

THE GUILLAIN-BARRÉ SYNDROME. R. FINLEY GAYLE and DALE GROOM, J. Nerv. & Ment. Dis. **98**:488 (Nov.) 1943.

Gayle and Groom review briefly the literature and the characteristic clinical picture of the Guillain-Barré syndrome. They report the case of a 4 year old child in whom complete flaccid quadriplegia, paralysis of the left abducens nerve, distended bladder, generalized hyperesthesia and absence of deep reflexes appeared three or four days after apparent recovery from an infection of the upper respiratory tract, in December 1942. A spinal tap on the fourth day in the hospital revealed 4 cells per cubic millimeter and a total protein content of 120 mg. per hundred cubic centimeters. Treatment according to the Kenny method was instituted, with local hot applications, manipulation, massage, exercises and use of removable casts. Recovery was progressive, and by September 1943 only some residual weakness and atrophy of the lower extremities remained. The authors believe the Kenny method to be of value in the treatment of this condition.

CHODOFF, Langley Field, Va.

CAUSES OF PAIN IN FEET AFTER PROLONGED IMMERSION IN COLD WATER. JAMES C. WHITE and SHIELDS WARREN, War Med. **5**:6 (Jan.) 1944.

Severe pain is common in the early and late stages of recovery from the results of prolonged immersion of the feet in cold water. On the basis of microscopic and other studies, White and Warren conclude that in the early phase of inflammation the pain is due to anoxia of the injured superficial tissues and nerve endings. Pain of this sort can be controlled by cooling the legs, as this procedure lowers cellular metabolism and makes the reduced demand for oxygen commensurate with the limited supply which can be furnished by the thrombosed superficial blood vessels.

After the period of inflammation has passed, aching pain and rigidity of the toes may cause prolonged incapacity in persons who have had more severe injury. This pain and rigidity are due to an increase in interstitial connective tissue and collagen. The nerves are embedded in fibrous tissue and show endoneural fibrosis. Pain of this type tends to ease after six to eight months, the time at which the collagen surrounding the nerves ceases to contract.

PEARSON, Philadelphia.

rosal and internal carotid nerves were interrupted by section of the facial or the greater superficial petrosal nerve. Two minute periods of hyperventilation, which had no effect on the electroencephalogram before section of the nerve, produced high potential slow waves after the nerve on one or on both sides was cut. Stimulation of the peripheral stumps of the nerves eliminated the slow waves. Intravenous administration of physostigmine likewise reduced or, eliminated these waves, and atropine increased them. Potentials recorded from the greater superficial petrosal nerve were in part of the type shown by other investigators to occur during autonomic regulation by the carotid sinus.

The presence of a parasympathetic cholinergic mechanism which counteracts the spasmodic effects of hypocapnia on the cerebral blood vessels seems to be indicated.

DISCUSSION

DR. WARREN S. McCULLOCH: Dr. Darrow commandeered one after another of the residents in brain surgery, and as each went to war, he took the next one. He and they did the work. This problem was a puzzling one. I had had an entirely different interpretation of the phenomenon in question, and I was more surprised than any one else at the outcome.

The principal place I filled was that of a "Doubting Thomas." My only contribution to the research was to insist that Dr. Darrow and his assistants actually demonstrate that the action potentials of the great superficial petrosal nerve diminished or disappeared prior to or during the appearance of the large slow brain waves induced by hyperventilation. This they did under my eyes. That, and only that, satisfied me as to the validity of the results.

But the society has a guest who knows far more about electroencephalograms than a tyro like me; I hope that Dr. Gibbs will have something to say about these observations.

DR. FREDERIC A. GIBBS: Dr. Darrow's recent paper (Am. J. Physiol. 140:583 [Jan.] 1944) gave a hint of the extraordinarily interesting observations that he has reported here. Therefore, although his results differ from those which my own work would have led me to expect, I am neither shocked nor unduly surprised. Perhaps it is a kindness that he has not emphasized the extent of this divergence. My co-workers and I have considered the carbon dioxide level in the brain one of the primary determinants of cortical frequency, whereas Dr. Darrow is able to explain the slowing that he obtains without much regard to this factor.

Dr. Lennox, Mrs. Gibbs and I have reported that the cerebral carbon dioxide tension, which we believe is of crucial importance to cortical function, is protected by a homeostatic mechanism that in most normal persons is extraordinarily competent. This mechanism is based on the response of the cerebral blood vessels to variations in carbon dioxide content. When a person hyperventilates, the arterial carbon dioxide drops precipitously, but there is not a corresponding drop in cerebral carbon dioxide, as indicated by blood returning from the brain; cerebral blood vessels constrict when the arterial carbon dioxide falls, with the result that the carbon dioxide produced by the brain accumulates and compensates for the drop in carbon dioxide in the arterial stream. It appears that when this mechanism is competent, overventilation does not ordinarily result in the extreme slowing of cortical potentials with an associated increase in amplitude which we have referred to as a "big build-up." On the other hand, when this homeostatic mechanism is defective, that is, when the cerebral blood vessels do not constrict adequately, a notable build-up tends to occur. Therefore, the crucial factor under these circumstances appears to be the competence of the cerebral vasoconstrictor mechanism. However, Dr. Darrow reports that by interfering with this constriction and by favoring cerebral vasodilation he prevents the occurrence of a great build-up. As stated before, this is exactly the opposite of what we should have expected.

Dr. Darrow's results are of the greatest interest. They require that we scrutinize our own results and conduct further experiments. The question involved is of more than academic interest. High voltage slow waves are commonly precipitated by overventilation in epileptic patients, and it is likely that this response is closely related to the pathologic physiology of the convulsive disorders.

DR. CHESTER DARROW: In reply to Dr. Gibbs, I do not believe there is real conflict between our results and the beautiful demonstration by him and his collaborators that slow waves during hyperventilation may be due to deficient homeostatic regulation of the carbon dioxide level in the brain. In fact, in experiments which led up to the present one we found that the fall in blood pressure associated with hyperventilation might provide sufficient regulation of blood flow, and consequently of cerebral carbon dioxide, to prevent change in the electroencephalogram. Increased alpha potential and, presumably, cerebral vasoconstriction might occur when the blood pressure stopped falling, but high potential slow waves did not appear unless there was also pronounced cardiac acceleration. Only if there was a notable increase of heart rate, suggestive of inhibition of parasympathetic activity, did we generally find high potential slow waves due to hyperventilation. Thus our results, like those of Dr. Gibbs, suggest that effective regulation of the cerebral carbon dioxide content, whether by decrease in blood pressure or by cerebral vasoconstriction, is not accompanied by high potential slow waves. Results of the present experiment indicate that the combination of low carbon dioxide and reduced supply of cholinergic substances is the condition most provocative of such waves. It is likely that homeostatic vasoconstrictor regulation of the cerebral blood flow by carbon dioxide is most uniform and effective when acetylcholine is present to prevent local, spasmodic and excessive effects of hypocapnia.

elayed early recognition of the tumor, and if suitable roentgenologic examination had revealed its site, surgical intervention would probably have been futile.

The case here reported is typical of chordoma arising from the region of the clivus, the second most common location of this tumor, the most common site being the sacrococcygeal junction.

DISCUSSION

DR. BEN W. LICHTENSTEIN: Although it is easy to diagnose chordoma from the autopsy specimen, great difficulty may be encountered with small surgical specimens. The cuboidal cells of chordoma resemble so much the cells of hypernephroma and some varieties of carcinoma that one often thinks of a metastatic tumor at the base of the brain. The policy of fixing the entire specimen in a solution of formaldehyde continues, as in the past, even though such fixation precludes detailed histochemical analysis for glycogen and other substances.

DR. VICTOR E. GONDA: I should like to ask about the triplopia. It would be easy to understand the presence of this sign if the third, as well as the sixth, nerve had been involved. Otherwise, as has been taught, monocular diplopia is always "functional." If triplopia may be due to involvement of the sixth nerve, the present concept will have to be revised.

Were the false images seen to the same side, or were they crossed?

DR. LLOYD H. ZIEGLER: Perhaps my experience may throw light on the triplopia which Dr. Bassoe mentioned. Several years ago I saw a patient who had been drinking too much and who was disoriented and had visual and auditory hallucinations. He declared that real objects before him appeared double or triple and in the horizontal plane. Aside from tremor and disorientation, one of the chief signs was slow, jerky horizontal nystagmus. He said that the hallucinatory images of dogs, camels, cats and strange people, which he feared, also appeared double and triple and in the horizontal plane. Within a few days after his coming to the hospital, the true and false sensory experiences and the nystagmus disappeared. Defects in several extraocular muscles might produce two or three kinds of diplopia and images which were out of their ordinary position. Triplopia is rare in my experience and is not easy to understand, unless the conditions mentioned in this case (chiefly the slow nystagmus) may throw light on it.

DR. PETER BASSOE: I cannot answer Dr. Gonda's question. I asked Dr. E. V. L. Brown about it. He did not see the patient until the diplopia had passed away. He says there is such a thing as monocular diplopia, to which one may add triplopia due to involvement of the sixth nerve.

Influence of Estrogen and Androgen on the Chemical Constituents of the Brain. DR. ARTHUR WEIL.

Three years ago attempts to determine chemical differences in the lipid composition of the brain of the male and of the female white rat were reported on before this society (Influence of Thyroid and Sex Glands on the Chemical Constitution of the Brain, ARCH. NEUROL. & PSYCHIAT. 46:547 [Sept.] 1941). It could be demonstrated then that at a given age (170 days) the phosphorus content of the alcoholic brain extracts, expressed as a percentage of the extract, was

higher in the brain of the female rat than in that of the male rat. Further investigations disclosed that for young animals before puberty these values were about the same (2.70 per cent) for the two sexes; however, the decrease to the adult level, which begins approximately at the time of sexual maturity, occurred more abruptly in the male brain.

An analysis of the different lipid fractions suggested that this difference in phosphorus content was due to an increase of the phosphorus content of the cephalin fraction of the female brain (The Chemical Growth of the Brain of the White Rat and Its Relation to Sex, Growth 7:257, 1943). Later I demonstrated, with Liebert (The Correlation Between Sex and Chemical Constitution of the Human Brain, Quart. Bull., Northwestern Univ. M. School 17:117, 1943) that similar sexual differences existed in the human brain.

The final proof that such differences are due to hormonal influences, and not to chromosomal determination alone, was furnished by experimental injection of estrogen and androgen into normal and into gonadectomized rats. If the homologous glandular substance was injected into young rats before maturity, no effect on the chemical constituents of the brain could be observed. Injections of androsterone into young female rats (25 days old), however, produced the chemical characteristics of a male brain and, vice versa, the young male brain was transformed chemically into a female brain by injection of estrogen. Injections after puberty did not produce such clearcut reversals. Removal of the gonads before puberty, however, followed by injections of a preparation containing the hormone of the opposite sex, gave transformations similar to those produced in normal, immature animals. The accompanying tabulation illustrates these results. White rats about 60 days old were given injections for seventy days.

Animal	Body Weight, Gm.	Brain Weight, Mg.	Alcoholic Extract		Cephalin Fraction	
			% of Dry Brain	% Phosphorus	% of Precipitate	% Phosphorus
Male.......	352	1,880	31.8	2.21	45.1	2.28
Female....	223	1,795	32.2	2.35	53.4	2.43
Castrate, given estrogen *	275	1,865	30.7	2.23	43.0	2.45
Spayed given androgen *	294	1,805	32.9	2.22	46.4	2.21

* The estrogen given was estradiol benzoate; the androgen used was testosterone propionate. Both substances were supplied by Ciba Pharmaceutical Products, Inc.

Parasympathetic Regulation of High Potentials in the Electroencephalogram. DR. CHESTER W. DARROW and DR. WARREN S. McCULLOCH and (by invitation) DR. JOHN R. GREEN, DR. EDWARD W. DAVIS and DR. HUGH W. GAROL.

The tendency for high potential slow waves appearing in the electroencephalogram during hyperventilation to be attended by an increase in heart rate suggested that the same autonomic mechanism might influence both the heart and the brain. It followed that if inhibition of vagal (parasympathetic) activity was the cause of the cardiac acceleration, section of parasympathetic pathways to the brain should increase high potential slow waves during hyperventilation.

Cats were operated on under ether anesthesia and then given beta erythroidine with artificial respiration. The parasympathetic pathways over the facial nerve, the geniculate ganglion and the greater superficial pet-

culture. He refers freely to his previous work in the field. He portrays the role of the medicine man in primitive society. The latter is frequently a psychotic or neurotic person, but one who has the capacity to utilize his peculiarities in such a way that he becomes a leader of his group. In addition, the author reports various libidinal situations that exist in certain primitive societies and traces their manifestations in the rituals, totems and taboos of the adults. He shows the direct relation of certain patterns of behavior in the group to libidinal situations created in the childhood of the members of these primitive societies. He briefly reviews the beginnings of the basic developments of civilization, such as agriculture. As an introduction to psychologic relations in primitive cultures the book is highly recommended. The reader should be aware that the book is not a volume of reference, but a brief presentation of the author's views and theories.

Manual of Psychological Medicine for Practitioners and Students. A. F. Tredgold. Price, $5. Pp. xi, plus 298. Baltimore: Williams & Wilkins Co., 1943.

The author of this volume is consulting physician to University College, London, and lecturer on mental deficiency at the London University. In his preface he states that the book is written because of the present need of general practitioners and students for information on psychiatric medicine. His desire is to create "a reasonably short, plain and practical account giving the essentials of this branch of medicine which would fill a very real wartime need." In this aim he has accomplished his purpose, for, in 298 pages, he has covered many of the essentials in the knowledge of practical psychiatry. The author has set down, both clearly and concisely, his concept of psychologic medicine in its entirety.

The usefulness of this book, however, is questionable. Like most compendiums, it covers too much ground, and too superficially. In the introduction, in which he discusses the "normal mind," theories of development and the darwinian concept of evolution are explained in elementary detail. The chapters dealing with the classification of "mental abnormality" and with general symptomatology are difficult to follow because there is no apparent theory behind the various classifications. Epilepsy is discussed under the heading of psychoneurosis, and Gowers is cited at great length, without any supplement from more recent work on either the neurophysiology or the clinical classifications of epilepsy. Similarly, in discussion of the major psychoses, one finds the concepts of Kraepelin and Bleuler, without mention of later investigators. The author differentiates sharply between the psychopathology of schizophrenia, a chronic hallucinatory psychosis, and dementia precox, a condition of primary mental decay.

Only 13 pages is devoted to therapy in any form, the major part of which is concerned with occupational therapy. Psychoanalysis is dealt with in 2 pages, in which the author's concept of the theories of Freud is set down and in which the results of psychoanalysis are stated to be questionable, impracticable and at times dangerous.

Finally, the major emphasis in the book is on the definitions of various forms of mental disease as designated by British law, and the various methods of commitment in England, neither of which can be of anything but academic interest to medical practitioners outside that country. To this reviewer, the book seems to contain an adequate presentation of the status of psychiatric practice several decades ago, and hence to be dangerous reading for the medical practitioner of today because of its omission of much that is at present important in the diagnosis and treatment of mental disease.

News and Comment

DIRECTORY OF MEDICAL SPECIALISTS CERTIFIED BY AMERICAN BOARDS 1945. PUBLISHED BY THE ADVISORY BOARD FOR MEDICAL SPECIALTIES

The biographic data of the first two editions of the "Directory of Medical Specialists" included only positions (internships, residencies or assistantships) held during the course of training of men up to the time of their certification by the American Boards, and positions on hospital and medical school staffs then currently held.

It is desired to extend these data in the third edition to include all formal appointments to hospitals and medical schools, with dates for which they were held, even though the appointee has now resigned, as well as records of all military service, including commissions and dates, whether in World War I, in the reserve forces in peacetime or in the present war.

Thus, a chronologically complete sketch of the entire career of a certified specialist is to be included in this third edition of the "Directory."

Membership or fellowship in national or sectional (not local) special societies and national general societies, with offices held and dates, should be reported.

Membership in recognized international medical societies may be included, but honorary or other membership in foreign medical societies should not be reported.

The certificate may refer to the second edition (1942) of the "Directory" for lists of medical societies to be included in his biographic sketch.

Families or secretaries of men absent in military service are asked to complete or correct previous listings or to prepare new forms now being mailed to physicians eligible for inclusion in the "Directory." Only persons certified by an official American Board can be included, and there is no charge for this listing.

This notice is published in response to many inquiries to assist physicians certified by the American Boards who are now engaged in correcting their previous listings or in preparing new sketches for the third edition of the "Directory," to be published early in 1945.

Communications should be addressed to the Director of Medical Specialists, 919 North Michigan Avenue, Chicago 11.

NEW SOCIETY IN HABANA

The Sociedad Cubana de Neurologia y Psiquiatria has been founded in Habana. The officers for the year are as follows: president, Dr. Rodolfo J. Guiral; first vice president, Dr. Jesús Cornide; second vice president, Dr. Julio Reymondez; secretary, Dr. José A. Bustamante; vice secretary, Dr. Oscar Sagredo; treasurer, Dr. Luis Muñiz Angulo; vice treasurer, Dr. Rafael Larragoiti.

Book Reviews

Recent Advances in Psychiatry. Special number of the *Journal of Mental Science*, published by authority of the Royal Medico-Psychological Association, January 1944. Volume 40. Price, 30 shillings. Pp. 509. London, J. & A. Churchill, Ltd.

This special number of the *Journal of Mental Science* is devoted to recent progress in psychiatry. An introduction by G. W. T. H. Fleming, managing editor, indicates that it is about fifteen years since Henry Devine issued his "Recent Advances in Psychiatry." The review covered in this volume is confined to work published during the five year period from 1938 to 1942, and in some instances the first half of 1943.

The authors hope to make this review a quinquennial publication. There are excellent surveys on problems of mental health · services, genetics, anatomy of the nervous system, physiologic psychology and electroencephalography. A section is devoted to biochemistry of the nervous system, written by Derek Richter. Other reviews are concerned with vitamin deficiency and the psychoses, neuroendocrine relationships, mental testing, psychopathology and neuropathology.

W. Mayer-Gross and Norman P. Moore have written an excellent review of the problem of schizophrenia. Aubrey Lewis gives a commendable survey of the problem of depression. Psychopathic personality is considered in a separate chapter by Curran and Mallinson. W. H. Gillespie brings the problems of the psychoneuroses up to date, and H. Crichton-Miller and Grace Nicolle have a useful review of psychotherapy. Other chapters are devoted to arteriosclerotic, senile and presenile psychoses, the psychiatric aspects of head injury, neurosyphilis, mental deficiency and child psychiatry. Convulsion therapy, prefrontal leukotomy and insulin therapy are given exhaustive consideration, and W. Norwood East and P. K. McCowan each have an excellent chapter on delinquency and crime and the legal aspects of psychiatry respectively.

This volume is a timely review, much needed and well done, and each chapter has an excellent bibliography for purposes of reference. The book is highly recommended, and one hopes that the publication of such reviews will be continued in the present, useful form.

Personality and the Behavior Disorders: A Handbook Based on Experimental and Clinical Research. Edited by J. McV. Hunt, Associate Professor of Psychology, Brown University. Price, $10. Volumes I and II. Pp. 618; 619-1242, with illustrations. New York: The Ronald Press Co., 1944.

These two volumes are the best collection of articles yet published on personality and behavior disorders. The editor indicates that the study of personality and its development must draw heavily on all of the biologic sciences. These books bring together the work of forty contributors, to give the major theories, facts and clinical experiences from the sciences relating to development of personality. As a result of the growing importance of the work of Galton, Freud, Pavlov and others, many scientific data have been accumulated in this field. Each chapter is written by an expert, and there is a minimal amount of technical jargon.

Volume I contains chapters on theoretic approaches to personality, dynamic theories of personality, methods of assessing personality, behavior dynamics and biologic and organic determinants of personality. Volume II is concerned with experimental and sociologic determinants of personality. Sections are devoted to outstanding patterns of behavior disorders and to investigate correlates of behavior disorders, and a closing section is concerned with therapy and the prevention of behavior disorders.

Many sections are excellent—for example, "The Physiological Effects of Emotional Tension," by Leon J. Saul; "Experimental Analysis of Psychoanalytic Phenomena," by Robert Sears; "The Conditioned Reflex Method and Experimental Neurosis," by H. S. Liddell, and "Experimental Studies of Conflict," by Neil E. Miller. William H. Sheldon contributes an excellent chapter on "Constitutional Factors of Personality." Nathan W. Shack has a first class chapter on "Physiological Effects in Behavior," and Stanley Cobb writes the excellent chapter entitled "Personality as Affected by Lesions of the Brain." Each of these men is an expert in his respective field, and the presentation is clear, concise and to the point.

Volume II continues with an excellent chapter by Margaret Ribbel on "Infantile Experience in Relation to Personality Development," a chapter by Gregory Bateson on "Cultural Determinants of Personality" and a section by Leo Kanner on "Behavior Disorders of Childhood." Lawson Lowrey wrote the section entitled "Delinquent and Criminal Personalities." Warren Stearns covers the problem of unit personalities in the military services in a timely, well written article. The psychoneuroses are discussed by William Malamud and the functional psychoses by Norman Cameron. Paul W. Prue is the author of the chapter "Psychopathic Personalities," and William G. Lennox discusses seizure states. The editor, J. McV. Hunt, writes the chapter "Psychological Deficit," and Kenneth Appel and George S. Stevenson contribute to the section "Therapy and the Prevention of Behavior Disorders."

These contributions attempt to correlate the many aspects of behavior disorders. They fill a long-standing want in the field of psychology and its relations to clinical psychiatry. More validated studies of normal personality function are needed in order better to evaluate clinical problems. It is apparent that much useful information can come from careful study of man and infrahuman forms in the uncovering of the dynamic laws of personality development.

This work is a truly collaborative product and is highly recommended as one of the most useful symposiums on this subject. It should be read by every psychologist, sociologist and neuropsychiatrist.

The Origin and Function of Culture. By Géza Róheim, Ph.D. Nervous and Mental Disease Monograph Series, No. 69. Price, $2.50. Pp. 103. New York: Nervous and Mental Disease Monographs. 1944.

Róheim discusses his subject from a strictly freudian point of view. He carefully indicates in the foreword that he is cognizant of the many other theories of the origin of culture and civilization but that he is presenting his explanation from the point of view of Eros.

Róheim delineates the role that prolongation of immaturity in human beings plays in the development of

culture. He refers freely to his previous work in the field. He portrays the role of the medicine man in primitive society. The latter is frequently a psychotic or neurotic person, but one who has the capacity to utilize his peculiarities in such a way that he becomes a leader of his group. In addition, the author reports various libidinal situations that exist in certain primitive societies and traces their manifestations in the rituals, totems and taboos of the adults. He shows the direct relation of certain patterns of behavior in the group to libidinal situations created in the childhood of the members of these primitive societies. He briefly reviews the beginnings of the basic developments of civilization, such as agriculture. As an introduction to psychologic relations in primitive cultures the book is highly recommended. The reader should be aware that the book is not a volume of reference, but a brief presentation of the author's views and theories.

Manual of Psychological Medicine for Practitioners and Students. A. F. Tredgold. Price, $5. Pp. xi, plus 298. Baltimore: Williams & Wilkins Co., 1943.

The author of this volume is consulting physician to University College, London, and lecturer on mental deficiency at the London University. In his preface he states that the book is written because of the present need of general practitioners and students for information on psychiatric medicine. His desire is to create "a reasonably short, plain and practical account giving the essentials of this branch of medicine which would fill a very real wartime need." In this aim he has accomplished his purpose, for, in 298 pages, he has covered many of the essentials in the knowledge of practical psychiatry. The author has set down, both clearly and concisely, his concept of psychologic medicine in its entirety.

The usefulness of this book, however, is questionable. Like most compendiums, it covers too much ground, and too superficially. In the introduction, in which he discusses the "normal mind," theories of development and the darwinian concept of evolution are explained in elementary detail. The chapters dealing with the classification of "mental abnormality" and with general symptomatology are difficult to follow because there is no apparent theory behind the various classifications. Epilepsy is discussed under the heading of psychoneurosis, and Gowers is cited at great length, without any supplement from more recent work on either the neurophysiology or the clinical classifications of epilepsy. Similarly, in discussion of the major psychoses, one finds the concepts of Kraepelin and Bleuler, without mention of later investigators. The author differentiates sharply between the psychopathology of schizophrenia, a chronic hallucinatory psychosis, and dementia precox, a condition of primary mental decay.

Only 13 pages is devoted to therapy in any form, the major part of which is concerned with occupational therapy. Psychoanalysis is dealt with in 2 pages, in which the author's concept of the theories of Freud is set down and in which the results of psychoanalysis are stated to be questionable, impracticable and at times dangerous.

Finally, the major emphasis in the book is on the definitions of various forms of mental disease as designated by British law, and the various methods of commitment in England, neither of which can be of anything but academic interest to medical practitioners outside that country. To this reviewer, the book seems to contain an adequate presentation of the status of psychiatric practice several decades ago, and hence to be dangerous reading for the medical practitioner of today because of its omission of much that is at present important in the diagnosis and treatment of mental disease.

News and Comment

DIRECTORY OF MEDICAL SPECIALISTS CERTIFIED BY AMERICAN BOARDS 1945. PUBLISHED BY THE ADVISORY BOARD FOR MEDICAL SPECIALTIES

The biographic data of the first two editions of the "Directory of Medical Specialists" included only positions (internships, residencies or assistantships) held during the course of training of men up to the time of their certification by the American Boards, and positions on hospital and medical school staffs then currently held.

It is desired to extend these data in the third edition to include all formal appointments to hospitals and medical schools, with dates for which they were held, even though the appointee has now resigned, as well as records of all military service, including commissions and dates, whether in World War I, in the reserve forces in peacetime or in the present war.

Thus, a chronologically complete sketch of the entire career of a certified specialist is to be included in this third edition of the "Directory."

Membership or fellowship in national or sectional (not local) special societies and national general societies, with offices held and dates, should be reported.

Membership in recognized international medical societies may be included, but honorary or other membership in foreign medical societies should not be reported.

The certificate may refer to the second edition (1942) of the "Directory" for lists of medical societies to be included in his biographic sketch.

Families or secretaries of men absent in military service are asked to complete or correct previous listings, or to prepare new forms now being mailed to physicians eligible for inclusion in the "Directory." Only persons certified by an official American Board can be included, and there is no charge for this listing.

This notice is published in response to many inquiries to assist physicians certified by the American Boards who are now engaged in correcting their previous listings or in preparing new sketches for the third edition of the "Directory," to be published early in 1945.

Communications should be addressed to the Directory of Medical Specialists, 919 North Michigan Avenue, Chicago 11.

NEW SOCIETY IN HABANA

The Sociedad Cubana de Neurologia y Psiquiatria has been founded in Habana. The officers for this year are as follows: president, Dr. Rodolfo J. Guiral; first vice president, Dr. Jesús Cornide; second vice president, Dr. Julio Reymondez; secretary, Dr. José A. Bustamante; vice secretary, Dr. Oscar Sagredo; treasurer, Dr. Luis Muñiz Angulo; vice treasurer, Dr. Rafael Larragoiti.

STUDIES ON DISEASES OF MUSCLE

I. PROGRESSIVE MUSCULAR DYSTROPHY; A CLINICAL REVIEW OF FORTY CASES

LIEUTENANT COMMANDER ROBERT E. SHANK (MC), U.S.N.R.[*]

AND

HELENA GILDER, M.D.[†]

AND

CHARLES L. HOAGLAND, M.D.

NEW YORK

Progressive muscular dystrophy is characterized by degeneration and atrophy of striated muscle. The disease is heredofamilial. It is accompanied by an abnormality in creatine metabolism, with creatinuria in adults or by excessive urinary excretion of creatine in children. Within recent years the study of diseases of muscle has received new impetus from several sources. New information concerning the origin and metabolism of creatine, the discovery of a deficiency disease in animals which resembles progressive muscular dystrophy in man and new knowledge of the physiology of muscle and the chemistry of muscle contraction have made it advisable to reexamine the syndrome of progressive muscular dystrophy in the light of these advances. This paper presents a clinical description and the results of preliminary studies of 40 cases of this disease.

Original descriptions of the syndrome of progressive muscular dystrophy are credited to Meryon, 1852,[1] and to Duchenne, 1861.[2] Erb[3] was the first to differentiate clearly between the muscular atrophies and the muscular dystrophies.

In 1884 he described a spinal form of muscular atrophy, which he attributed to degeneration of the anterior horn cells, and a syndrome of muscular dystrophy, in which no such changes in the central nervous system were demonstrable.

Various clinical forms of muscular dystrophy have been described. Erb,[3] in 1884, reported on a juvenile type which differed from the syndrome described by Duchenne in that the onset occurred later in childhood and atrophy of the skeletal muscles was not accompanied by pseudohypertrophy. A facioscapulohumeral form which included involvement of the facial musculature, as well as the changes associated with the juvenile type of Erb, was described by Landouzy and Dejerine.[4] The earliest descriptions of muscular dystrophy characterized the disease as involving only the proximal muscles of the extremities, with sparing of the distal muscles of the hands, forearms and feet. However, Gowers,[5] in 1902, and Spiller,[6] in 1907, recognized a form of the disease with early changes in the distal musculature. Gowers,[7] in his monograph on pseudohypertrophic muscular paralysis, published in 1879, stated that "hypertrophy and atrophy may exist in different proportions and there are cases which connect the two extremes —in some enlargement of many muscles, and in others wasting of all." Erb[8] expressed the

1. Meryon, E.: On Granular and Fatty Degeneration of the Voluntary Muscles, Med.-Chir. Tr., London 35:73, 1852.

2. Duchenne, G. B. A.: Paraplégie hypertrophique congenitale: De l'électrisation localisée et son application à la pathologie et à la therapeutique, ed. 2, Paris, J.-B. Baillière et fils, 1861.

3. Erb, W.: Ueber die "juvenile Form" der progressiven Muskelatrophie und ihre Beziehungen zur sogenannten Pseudohypertrophie der Muskeln, Deutsches Arch. f. klin. Med. 34:467 (March 27) 1884.

4. Landouzy, L., and Dejerine, J.: De la myopathie atrophique progressive (myopathie héréditaire débutant, dans l'enfance, par la face, sans altération du système nerveux), Compt. rend. Acad. d. sc. 98:53 (Jan. 7) 1884.

5. Gowers, W. R.: A Lecture on Myopathy and a Distal Form, Brit. M. J. 2:89 (July 12) 1902.

6. Spiller, W. G.: Myopathy of the Distal Type and Its Relation to the Neural Form of Muscular Atrophy (Charcot-Marie-Tooth Type), J. Nerv. & Ment. Dis. 34:14, 1907.

7. Gowers, W. R.: Pseudohypertrophic Muscular Paralysis, London, J. & A. Churchill, 1879.

8. Erb, W.: Dystrophia muscularis progressiva, Deutsche Ztschr. f. Nervenh. 1:173 (July 24) 1891.

431

opinion that all the clinical forms of muscular dystrophy were variations in manifestation of the same disease process. Such a view is still tenable, and clinical classifications of the disease are useful only in designating the muscle groups first affected and the age of onset of the disease.

The degenerative changes in progressive muscular dystrophy are extensive and are usually limited to skeletal muscle, although the myocardium may be involved.[9] Smooth muscle of the gastrointestinal tract and of other organs is believed to be unaffected. Pseudohypertrophy develops most commonly in large, bulky muscles, such as the soleus, gastrocnemius, gluteus, deltoid, supraspinatus and infraspinatus muscles and the muscles of the tongue. The increase in size of these muscles is due chiefly to an increase in the fat and connective tissue elements.

The muscles affected by dystrophy are pale. Microscopic changes are essentially the same in all forms of the disease. The fibrous connective tissue and the fat between the muscle bundles are increased in amount. Muscle fibers are decreased in diameter and in number and in many instances show longitudinal splitting. Accumulations of nuclei appear beneath the sarcolemmal sheaths. Within the fibers signs of degeneration are evidenced by vacuolation and by hyalinoid and granular changes. In late stages of the disease the muscle is almost completely replaced and only occasional muscle fibers may be seen.

DATA ON CASES

Forty patients comprised the series studied. All the patients had been seen previously in other clinics or by other physicians and referred to the Hospital of the Rockefeller Institute for Medical Research with the diagnosis of progressive muscular dystrophy. Patients for whom the diagnosis could not be confirmed were not included in this series. The criteria utilized in making the diagnosis of progressive muscular dystrophy were as follows: (a) a history of progressive muscular weakness and disability, (b) occurrence of other cases of the disease in the same family; (c) demonstrable atrophy or pseudohypertrophy of affected muscles, (d) hypoactivity or absence of tendon reflexes, (e) absence of signs referable to disease of the central nervous system and (f) creatinuria, in an adult, or increased excretion of creatine, in a child. Most of these patients have been followed clinically for from one to three years.

9. (a) Sachs, B., and Brooks, H.: Progressive Muscular Dystrophy, with the Report of an Autopsy, Am. J. M. Sc. **122**:54 (July) 1901. (b) Bunting, C. H.: Chronic Fibrous Myocarditis in Progressive Muscular Dystrophy, ibid. **135**:244 (Feb.) 1908. (c) Globus, J. H.: The Pathologic Findings in the Heart Muscle in Progressive Muscular Dystrophy, Arch. Neurol. & Psychiat. **9**:59 (Jan.) 1923. (d) Yoshida, T.: Ueber die Myokardveränderung bei der progressiven Muskeldystrophie, Jap. J. M. Sc., V, Path. **5**:63 (March) 1940.

Sex Distribution.—Progressive muscular dystrophy has been shown to occur more frequently in males. In the series of cases reviewed by Gowers[7] there were 190 males and 30 females. Hough[10] reported a series of 28 cases in which there were no females. In the cases studied by Hurwitz,[11] 6 of 44 patients were females. Bell,[12] in a review of 1,324 cases reported in the literature, found that 73.1 per cent were males. Of the 40 patients included in the group described here, 35 were males and 5 females.

Age Distribution.—The youngest patient was 2½ and the oldest 57 years of age. The age distribution of the patients is shown in table 1.

TABLE 1.—*Age Distribution of Patients*

Age, Years	0-5	6-10	11-15	16-20	21-30	31-40	41-50	51-60
No. of patients	5	14	2	3	4	9	1	2

It will be seen that 19 patients, or 47.5 per cent of the series, were less than 10 years of age.

Racial, National and Social Representation.—Muscular dystrophy occurs rarely in Negroes. Pearson[13] illustrated the case of a Negro boy, and Orbison[14] reported a case in a Negro woman. One Negro boy was included in the present series.

Most of the patients were inhabitants of the city of New York and were derived from family groups representing Russian, Italian, Hungarian, German, Irish, Lithuanian, Austrian and English nationalities. Thirteen of the 40 patients were of Jewish extraction. The percentage of patients derived from each of these national groups corresponded roughly with the distribution of these groups in the population of New York.

The patients represented all social levels. There was no evidence that the disease was more prevalent among the underprivileged. The histories indicated that the diets had been adequate, and unusual food habits were infrequent.

10. Hough, G. de N., Jr.: Progressive Pseudohypertrophic Muscular Dystrophy: Report of the Results of Treatment with Adrenalin and Pilocarpin, with Analysis of Twenty-Eight Cases, J. Bone & Joint Surg. **13**:825 (Oct.) 1931.

11. Hurwitz, S.: Primary Myopathies: Report of Thirty-Six Cases and Review of the Literature, Arch. Neurol. & Psychiat. **36**:1294 (Dec.) 1936.

12. Bell, J.: On Pseudohypertrophic and Allied Types of Progressive Muscular Dystrophy, in Fischer, R. A.: The Treasury of Human Inheritance, London, Cambridge University Press, 1943, vol. 4, pt. 4.

13. Pearson, K.: Two New Pedigrees of Muscular Dystrophy, Ann. Eugenics **5**:179 (Jan.) 1933.

14. Orbison, T. J.: Myopathy, with Clinical Records of Eight Cases Comprising Various Types, Am. J. M. Sc. **148**:550 (Oct.) 1914.

STUDIES ON DISEASES OF MUSCLE

I. PROGRESSIVE MUSCULAR DYSTROPHY; A CLINICAL REVIEW OF FORTY CASES

LIEUTENANT COMMANDER ROBERT E. SHANK (MC), U.S.N.R.*

AND

HELENA GILDER, M.D.†

AND

CHARLES L. HOAGLAND, M.D.

NEW YORK

Progressive muscular dystrophy is characterized by degeneration and atrophy of striated muscle. The disease is heredofamilial. It is accompanied by an abnormality in creatine metabolism, with creatinuria in adults or by excessive urinary excretion of creatine in children. Within recent years the study of diseases of muscle has received new impetus from several sources. New information concerning the origin and metabolism of creatine, the discovery of a deficiency disease in animals which resembles progressive muscular dystrophy in man and new knowledge of the physiology of muscle and the chemistry of muscle contraction have made it advisable to reexamine the syndrome of progressive muscular dystrophy in the light of these advances. This paper presents a clinical description and the results of preliminary studies of 40 cases of this disease.

Original descriptions of the syndrome of progressive muscular dystrophy are credited to Meryon, 1852,[1] and to Duchenne, 1861.[2] Erb[3] was the first to differentiate clearly between the muscular atrophies and the muscular dystrophies.

In 1884 he described a spinal form of muscular atrophy, which he attributed to degeneration of the anterior horn cells, and a syndrome of muscular dystrophy, in which no such changes in the central nervous system were demonstrable.

Various clinical forms of muscular dystrophy have been described. Erb,[3] in 1884, reported on a juvenile type which differed from the syndrome described by Duchenne in that the onset occurred later in childhood and atrophy of the skeletal muscles was not accompanied by pseudohypertrophy. A facioscapulohumeral form which included involvement of the facial musculature, as well as the changes associated with the juvenile type of Erb, was described by Landouzy and Dejerine.[4] The earliest descriptions of muscular dystrophy characterized the disease as involving only the proximal muscles of the extremities, with sparing of the distal muscles of the hands, forearms and feet. However, Gowers,[5] in 1902, and Spiller,[6] in 1907, recognized a form of the disease with early changes in the distal musculature. Gowers,[7] in his monograph on pseudohypertrophic muscular paralysis, published in 1879, stated that "hypertrophy and atrophy may exist in different proportions and there are cases which connect the two extremes —in some enlargement of many muscles, and in others wasting of all." Erb[8] expressed the

1. Meryon, E.: On Granular and Fatty Degeneration of the Voluntary Muscles, Med.-Chir. Tr., London 35:73, 1852.

2. Duchenne, G. B. A.: Paraplégie hypertrophique congénitale: De l'électrisation localisée et son application à la pathologie et à la therapeutique, ed. 2, Paris, J.-B. Baillière et fils, 1861.

3. Erb, W.: Ueber die "juvenile Form" der progressiven Muskelatrophie und ihre Beziehungen zur sogenannten Pseudohypertrophie der Muskeln, Deutsches Arch. f. klin. Med. 34:467 (March 27) 1884.

4. Landouzy, L., and Dejerine, J.: De la myopathie atrophique progressive (myopathie héréditaire débutant, dans l'enfance, par la face, sans altération du système nerveux), Compt. rend. Acad. d. sc. 98:53 (Jan. 7) 1884.

5. Gowers, W. R.: A Lecture on Myopathy and a Distal Form, Brit. M. J. 2:89 (July 12) 1902.

6. Spiller, W. G.: Myopathy of the Distal Type and Its Relation to the Neural Form of Muscular Atrophy (Charcot-Marie-Tooth Type), J. Nerv. & Ment. Dis. 34:14, 1907.

7. Gowers, W. R.: Pseudohypertrophic Muscular Paralysis, London, J. & A. Churchill, 1879.

8. Erb, W.: Dystrophia muscularis progressiva, Deutsche Ztschr. f. Nervenh. 1:173 (July 24) 1891.

All the patients had visited other clinics and had been treated by other physicians. Many types of therapy had been attempted, without improvement or arrest of the disease in any case. In table 3 are listed the therapeutic agents used and the number of patients receiving each form of treatment. .

TABLE 3.—*Therapeutic Agents Used Prior to Beginning of This Study*

Type of Therapy	Number of Patients Treated
Amino acids	
Aminoacetic acid	14
Aminoacetic acid and ephedrine	5
Gelatin	3
Vitamins	
Thiamine	8
Riboflavin	4
Nicotinic acid	3
Pyridoxine	17
Ascorbic acid	2
Alpha tocopherol	17
Wheat germ oil	11
Glandular preparations	
Gonadotropin	3
Epinephrine and pilocarpine	3
Adrenal cortex extract	1
Androgen	1
Parathyroid extract	1
Miscellaneous agents	
Creatine	1
Potassium chloride	2
Amphetamine	2
Unsaturated fatty acids	2
Bile salts and bile salts and iron	1
Massage	10
Electrical stimulation	3
Hydrotherapy	5

PHYSICAL SIGNS

Physical examinations of the 40 patients in this series revealed various distributions of affected muscle groups and all stages in the course of the disease. Pseudohypertrophy was seen frequently in the younger patients and infrequently in the older ones. In many of the patients both pseudohypertrophy and atrophy existed in different groups of muscles. The muscles most commonly exhibiting pseudohypertrophy were the soleus, gastrocnemius, gluteus, deltoid, infraspinatus and supraspinatus muscles.

Involvement of muscles about the shoulder girdles produced characteristic winging of the scapulas. Lumbar lordosis was prominent when the muscles about the vertebral column and the extensors of the thighs were involved, a deformity that was pronounced in 21 patients. In 18 patients the atrophic process in the muscles of the calves produced shortening of the achilles tendon and talipes equinovarus. When muscles of the lower extremities were affected, there was a characteristic gait in which the feet were slapped down and the hips were shifted one ahead of the other to effect a forward motion.

All the younger patients showed the sign of Gowers,[7] who described the movements necessary for persons with this disease to rise from a

sitting position on the floor to a standing position. The patient turns over, supports himself on his hands and knees and, extending his legs at his knees, pushes himself gradually upward by placing his hands successively on his ankles, knees and hips.

Five of the 40 patients exhibited enlargement of the tongue. Each of these 5 patients also had involvement of the facial musculature, with a resultant transverse smile.

Fibrillary twitchings were not seen in the muscles of any of the patients. The superficial reflexes were normal. The tendon reflexes were hypoactive or absent, except that early in the involvement of the muscles of the calf the achilles tendon reflex was often hyperactive. There were no signs of an upper motor neuron defect.

Boas and Lowenburg [20] and Hurwitz [11] described pronounced tachycardia, with lability of the heart rate and excessive response to minimal stimuli in the patients whom they observed. The pulse rate during rest was characteristically high in the 40 patients of the present series. The pulse and temperature chart of 1 patient is reproduced in the figure.

Sachs and Brooks,[9a] Bunting [9b] and Globus [9c] reported on involvement of the myocardium by the dystrophic process. In 2 patients in the present series without previous signs or history of heart disease cardiac decompensation slowly developed, with dilatation of the heart. Roentgenograms showed a large, dilated heart, with limited movement of the ventricles in the roentgenokymogram. One of these patients had changes in the electrocardiogram suggestive of myocardial damage. Digitalization resulted in the disappearance of signs of decompensation.
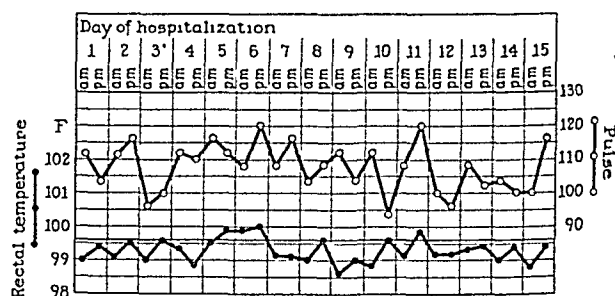
Tachycardia in a case of progressive muscular dystrophy.

Attempts to discontinue the use of digitalis were followed by the return of cardiac decompensation. Both these patients had widespread atrophy of most of the muscles of the extremities. It is likely that degenerative changes had also occurred in the myocardium.

20. Boas, E. P., and Lowenburg, H.: The Heart Rate in Progressive Muscular Dystrophy, Arch. Int. Med. **47:**376 (March) 1931.

Genetic Influences.—Meryon,[15] in 1866 and Gowers[7] in 1879, called attention to the factor of heredity in progressive muscular dystrophy. Bell[12] found genetic influences in 79 per cent of 1,341 cases recorded in the literature and reported that 47 of 114 cases in the National Hospital, Queens Square, London, occurred in families in which other cases had appeared. Genetic patterns have been found to be of various types, the disease following dominant, sex-linked or recessive factors. Weitz[16] noted that the dominant mode of transmission was accompanied by more frequent involvement of the muscles of the upper extremities, whereas the genetic patterns of muscular dystrophy with onset in childhood and involvement of the muscles of the calves and thighs were more likely to be recessive. Bell[17] found no evidence of earlier onset of the disease in later generations of families in which the disease occurred. Twenty-six of the 40 patients in our series were the only members with the disease in their respective families. However, many of the patients were unable to construct pedigrees including more than three generations. For 2 of the 14 patients from families in which other cases of progressive muscular dystrophy had occurred the disease was mediated through a dominant gene; for 5, through a sex-linked gene, and for 7, through a simple recessive gene.

Conditioning Factors in the Causation of the Disease.—It has been reported that the onset of progressive muscular dystrophy may follow infectious disease,[18] trauma[19] and overexertion.[19a] Only 5 of the 40 patients had a history of factors of this type. Two patients first showed signs of the disease after attacks of acute poliomyelitis. The mother of 1 patient had congenital syphilis. She had received antisyphilitic therapy in childhood, and the Wassermann reaction had been

negative for many years prior to the birth of the child. The patient's Wassermann reaction was negative. Another patient had sustained an injury at birth. In 1 patient the first signs of the disease were noted after pregnancy.

Age of Onset.—The age of onset of the disease in this series of patients as determined by the time of appearance of the first symptoms is recorded in table 2. Twenty-five patients, or 62

TABLE 2.—*Age of Patients at Onset of Disease*

Age, Years	0-5	6-10	11-15	16-20	21-30	31-40	41-50
No. of patients	22	3	4	2	6	2	1

cent of the series, noted the first symptoms before the age of 10 years. In all of these patients the earliest signs of the disease were referable to changes in the muscles of the thighs and calves. Of the 15 patients whose muscular disabilities became apparent after the age of 10 years, 5 complained first of weakness of and noted atrophy in the scapulohumeral group of muscles.

Clinical Course of the Disease.—In each of the 40 patients the dystrophic process appearing in one or more muscles progressed to involve other groups of muscles. The progress of the disease was most rapid in persons in whom the disease had its onset in infancy or early childhood. Of 22 patients in whom the first signs of the disease were noted before the age of 5 years, 8 were invalids and unable to walk by the age of 10 years, and the condition of 3 others had progressed to complete invalidism by the age of 15 years. Of the 15 patients in whom the disease had its onset after the age of 10 years, the condition of only 3 had progressed to complete invalidism twelve, sixteen and twenty-eight years, respectively, after the appearance of the first symptoms.

A complaint of cramping pains occurring early in the course of the disease in the affected muscles of the extremities and in the abdominal muscles was made by 14 patients. The pains were severe enough to keep the patients awake at night, and in the case of 1 patient the symptom led to a faulty diagnosis of acute appendicitis. There seemed to be no relation between prior use of the muscles and the onset of the pain. Spasm of the muscles at the site of the pain was observed in 1 patient, but the pain was usually unaccompanied by demonstrable muscular spasm. No mention of the occurrence of this symptom in cases of muscular dystrophy has been found in the medical literature, although pain was a frequent complaint in the present series.

15. Meryon, E.: On Granular Degeneration of the Voluntary Muscles, Med.-Chir. Tr., London **49**:45, 1866.

16. Weitz, W.: Ueber die Vererbung bei der Muskeldystrophie, Deutsche Ztschr. f. Nervenh. **72**:143 (Sept.) 1921.

17. Bell, J.: On the Age of Onset and Age at Death in Hereditary Muscular Dystrophy, with Some Observations Bearing on the Question of Antedating, Ann. Eugenics **11**:272 (May) 1942.

18. (*a*) Kaumheimer, L.: Progressive Muskeldystrophie nach (rezidivierender) Poliomyelitis, Ztschr. f. Kinderh. **25**:1 (May 8) 1920. (*b*) Gaupin, C. E.: Symposium on Muscular Dystrophies, Kentucky M. J. **23**:523 (Nov.) 1925. (*c*) Barnes, S.: A Myopathic Family, with Hypertrophic, Pseudohypertrophic, Atrophic and Terminal (Distal in Upper Extremities) Stages, Brain **55**:1 (March) 1932.

19. (*a*) Arbuse, D. I., and Sloane, D.: Muscular Dystrophy: Report of a Family, New York State J. Med. **37**:1111 (Jan. 15) 1937. (*b*) Gaupin.[19b] (*c*) Barnes.[19c]

firmed the earlier reports of decrease in urinary creatinine. Levene and Kristeller [32] first demonstrated that creatinuria usually accompanies the disease.

There were an increase in the creatine excretion and a decrease in the creatinine excretion of all the patients in this series. The rate of excretion of these substances was studied for 9 boys with muscular dystrophy between the ages of 6 and 11 years. This rate was compared with the rate of excretion for 5 normal boys of the same age group. The diets of all the subjects were similar and provided 3 Gm. of protein, 2 Gm. of fat and 6 Gm. of carbohydrate per kilogram of body weight per day. The foods containing precursors of creatine and creatinine were contained in constant and like amounts in all the diets. The amounts of creatine and creatinine in twenty-four hour specimens of urine were determined by a modification of Folin's [30] method, in which the photoelectric colorimeter was utilized. The results presented in table 4 include the average daily rates of excretion of creatine and creatinine

TABLE 4.—*Daily Excretion of Creatine and Creatinine in Normal Subjects and in Patients with Muscular Dystrophy*

Subject	Age, (Years)	Period of Study (Days)	Creatine as Creatinine, Average Daily Excretion (Mg. per Kilogram of Body Weight per Day)	Creatinine, Average Daily Excretion (Mg. per Kilogram of Body Weight per Day)
Normal Subjects				
J. B.	9	11	15.8	18.9
S. B.	11	9	9.7	19.6
R. D.	12	10	5.6	22.6
W. S	9	13	14.1	22.6
L. V.	11	11	9.2	24.2
Average			10.9	21.6
Patients with Muscular Dystrophy				
A. G.	8	13	18.8	13.1
R. G.	8	34	17.1	10.3
R. R.	5	32	16.7	18.7
D. W. S.	7	39	21.9	11.6
A. T.	11	17	23.0	9.5
G. T.	7	43	19.2	10.0
R. B.	6	15	20.0	14.0
D. S.	7	16	30.1	9.2
R. D. G.	11	15	33.7	13.7
Average			22.3	12.2

during the periods studied. The values for creatine represent creatine determined as creatinine.

Normal boys excreted from 5.6 to 15.8 mg. of creatine per kilogram of body weight per day on the diet indicated, an average of 10.9 mg per kilogram per day, while the boys with muscular dystrophy excreted daily from 16.7 to 33.7 mg.

32. Levene, P. A., and Kristeller, L.: Factors Regulating the Creatinin Output in Man, Am. J. Physiol. **24**:45 (April) 1909.

of creatine per kilogram of body weight, an average of 22.3 mg. per kilogram per day. Excretion of creatinine was greater for the normal boys, with an average daily urinary excretion of 21.6 mg. per kilogram and with rates of excretion varying from 18.9 to 24.2 mg. per kilogram. The average rate of excretion of creatinine for the patients with progressive muscular dystrophy was 12.2 mg. per kilogram per day, with extremes of 9.2 and 14 mg. per kilo-

TABLE 5.—*Fasting Plasma Concentrations and Urinary Excretion Rates of Creatine and Creatinine in Normal Subjects and in Patients with Muscular Dystrophy*

Subject	Age (Years)	Plasma Concentration		Urinary Excretion Rate	
		Creatine as Creatinine (Mg./100 Cc.)	Creatinine (Mg./100 Cc.)	Creatine as Creatinine (Mg. per Kilogram of Body Weight per Day)	Creatinine (Mg. per Kilogram of Body Weight per Day)
Normal Subjects					
L. V.	11	0.95	0.85	4.7	22.3
S. B.	11	0.74	0.86	3.7	22.3
W. S.	9	0.99	0.69	5.6	23.9
R. D.	12	1.06	0.70	4.3	13.1
J. B.	9	1.07	0.74	6.0	19.6
Average		0.96	0.77	5.0	19.7
Patients with Muscular Dystrophy					
A. T.	11	1.11	0.68	14.1	7.2
R. R.	7	1.17	0.67	15.5	6.9
D. W. S.	7	1.24	0.66	10.9	8.9
R. G.	8	1.24	0.67	14.1	7.4
A. G.	8	1.02	0.93	14.7	11.4
Average		1.16	0.72	13.8	8.3

gram per day. Excretion of creatine for dystrophic patients was 204 per cent that of control children of the same sex and age group, whereas excretion of creatinine was only 56 per cent of the output of the control subjects.

When the subjects fasted for twenty-four hours to eliminate the effects of an intake of small amounts of precursors of creatine on creatine excretion, the differences were more pronounced. During the fasting period the rate of excretion of creatine and creatinine was determined for 5 boys with muscular dystrophy and for 5 normal boys. The fasting concentrations of creatine and creatinine in the plasma were also determined. The results are recorded in table 5.

In the fasting state, the average rate of excretion of creatine for the dystrophic patients was 282 per cent of the rate for the control subjects. The rate of excretion of creatinine was 42 per cent of that for the control group. The fasting concentration of creatine in the plasma was higher for the patients with muscular dystrophy, the average concentration being 1.16 mg. per hundred cubic centimeters, as compared with an

Gowers [7] described a reddish purple mottling of the skin which frequently accompanied progressive muscular dystrophy. This phenomenon was noted in all the younger patients and in many of the adults in our series. It was most pronounced in the skin over the lower half of the body.

The disease in its late stages frequently manifests lipodystrophy, large deposits of soft fat accumulating about the face, neck, hips and thighs. This change was conspicuous in 9 patients of the present series. Although all these patients had extensive muscular atrophy, the deposition of fat prevented the appearance of emaciation and aided in the maintenance of body contours.

Electrocardiographic Changes.—Electrocardiograms were taken at frequent intervals on all these patients. All of the records showed a rapid heart rate with normal or irregular sinus rhythm. No other electrocardiographic changes occurred with any frequency. In a patient who previously had shown left axis deviation right axis deviation developed, with lengthening of the Q-T interval, prior to the development of cardiac dilatation and decompensation. The results of a study of the electrocardiograms of these patients are to be reported in detail by Newman, Shank, Hoagland and Cohn.[21]

Roentgenograms.—Atrophy and malformations of bone have been described as part of the disease process in progressive muscular dystrophy by Wright [22]; Janney, Goodhart and Isaacson [23]; Hurwitz [11]; Maybarduk and Levine,[24] and Epstein and Abramson.[25] Roentgenograms were made of the skull, heart, lungs, vertebral column, pelvis, long bones, hands and feet of each of the 40 patients. There was streaking of the soft tissue shadows of affected muscles which was due to the contrasting mediums of muscle and of the infiltrating connective tissue and fat. The appearance of centers of ossification in the bones of the hands and in the epiphyses of the long bones was delayed. Evidences of demineralization were apparent in the bony structure of most of the patients. These changes were frequent and were considered characteristic of progressive muscular dystrophy. They will be described in detail in a later paper.

Other roentgenographic changes occurred less frequently and were considered incidental to the disease. Timme [26] reported early calcification of the pineal gland in cases of progressive muscular dystrophy. In our series 2 patients less than 20 years of age had calcification of the pineal body. One adult had a greatly enlarged sella turcica, with roentgenographic evidence of a pituitary adenoma. Two young adults had pronounced hyperostosis frontalis interna. There was roentgenographic evidence of pulmonary tuberculosis with cavitation in 1 patient and of pronounced cardiac hypertrophy in a patient with a history of rheumatic heart disease.

METABOLIC STUDIES

Twenty-two of the 40 patients were observed during periods of hospitalization in a metabolism ward. The rate of urinary excretion of creatine and creatinine, the fasting level of creatine and creatinine in the blood, the basal metabolic rate, the dextrose tolerance and the balance of nitrogen and of phosphorus were determined.

Rate of Urinary Excretion of Creatine and Creatinine.—The reports of numerous investigators have shown that changes in creatine and creatinine metabolism occur in progressive muscular dystrophy and that the increase in creatine output is to some extent proportional to the amount of affected musculature. Rosenthal,[27] in 1870, reported a decreased excretion of creatinine, an observation also made by Weiss,[28] in 1877, and by Langer,[29] in 1882. With the development of an improved method for the estimation of creatine and creatinine by Folin,[30] in 1904, more exact studies were made possible. Spriggs [31] con-

21. Newman, C.; Shank, R. E.; Hoagland, C. L., and Cohn, A. E.: The Electrocardiogram in Progressive Muscular Dystrophy, to be published.

22. Wright, C.: Consideration of Progressive Muscular Dystrophy with Pseudohypertrophy from an Endocrine Standpoint, California & West. Med. **23:** 999 (Aug.) 1925.

23. Janney, N. W.; Goodhart, S. P., and Isaacson, V. I.: The Endocrine Origin of Muscular Dystrophy, Arch. Int. Med. **21:**188 (Feb.) 1918.

24. Maybarduk, P. K., and Levine, M.: Osseous Atrophy Associated with Progressive Muscular Dystrophy, Am. J. Dis. Child. **61:**565 (March) 1941.

25. Epstein, B. S., and Abramson, J. L.: Roentgenologic Changes in the Bones in Cases of Pseudohypertrophic Muscular Dystrophy, Arch. Neurol. & Psychiat. **46:**858 (Nov.) 1941.

26. Timme, W.: Progressive Muscular Dystrophy as an Endocrine Disease, Arch. Int. Med. **19:**79 (Jan.) 1917.

27. Rosenthal, M.: Handbuch der Diagnostik und Therapie der Nervenkrankheiten, Erlangen, F. Enke, 1870, p. 220.

28. Weiss, N.: Ueber einen Fall von progressiver Muskelatrophie, Wien. med. Wchnschr. **27:**701, 1877.

29. Langer, L.: Ein Fall von ausgebreiteter progressiver Muskelatrophie mit paralytischer Lendenlordose, Deutsches Arch. f. klin. Med. **32:**395 (Dec. 18) 1882.

30. Folin, O.: Beitrag zur Chemie des Kreatinins und Kreatins im Harne, Ztschr. f. physiol. Chem. **41:** 223 (March 5) 1904.

31. Spriggs, E. I.: The Excretion of Creatinin in a Case of Pseudo-Hypertrophic Muscular Dystrophy, Biochem. J. **2:**206, 1907.

The median basal metabolic rate for the group of 14 patients was —14.5 per cent of the normal standards. Individual rates varied from —24 to +10 per cent. The results indicate that progressive muscular dystrophy is usually accompanied by a decrease in the basal metabolic rate.

INTRAVENOUS DEXTROSE TOLERANCE TEST

Abnormalities of carbohydrate metabolism in patients with progressive muscular dystrophy have been described by various investigators. McCrudden and Sargent,[38] Byard, [39] and Brock and Kay [40] observed low fasting levels of the blood sugar. McCrudden [41] expressed the opinion that the abnormality in dextrose metabolism is a causative factor in the malfunction of the diseased muscle. With oral dextrose tolerance tests, Janney, Goodhart and Isaacson [23] observed delayed utilization of dextrose. Hurwitz [11] and Magee,[42] however, reported an increased rate of utilization of dextrose when given by mouth. Scheman, Lewin and Soskin [43] and Elkington and Goldblatt [44] obtained normal responses to test doses of dextrose given orally.

Intravenous dextrose tolerance tests were performed on 9 patients with progressive muscular dystrophy and on 5 normal subjects. All of the subjects were made to fast for twelve hours prior to the administration of dextrose. Within ten minutes 0.5 Gm. of dextrose per kilogram of body weight was given intravenously as a 20 per cent solution in 0.9 per cent solution of sodium chloride. Fasting samples of blood were obtained, and samples were taken five, fifteen, thirty, forty-five, sixty, seventy-five and ninety minutes after completion of the venoclysis. The level of sugar in whole blood was determined by the method of Miller and Van Slyke.[45] Responses to intravenous injection of the dextrose solution are recorded in table 8.

In all the patients and the control subjects the sugar concentration of the blood had returned to fasting levels within seventy-five minutes of the administration of dextrose. In 1 subject there was evidence of rapid utilization of dextrose, the level of sugar in the blood dropping to 68 mg. per hundred cubic centimeters in thirty minutes and to 44 mg. per hundred cubic centimeters in ninety minutes. There were no clinicals signs of hypoglycemia in this or any other of the patients. The average fasting level of blood sugar was somewhat lower in the patients with muscular dystrophy, being 76.4 mg. per hundred cubic centimeters, as compared with an average fasting concentration of 85.4 mg. per hundred cubic centimeters for the 5 normal subjects. Average blood sugar levels at the various intervals following injection gave no indication of an increased or a decreased rate of utilization of dextrose in the dystrophic patients. With the single exception previously described, all dystrophic patients and control subjects gave responses to intravenous administration of dextrose within the normal limits for age and sex described by Crawford.[46]

NITROGEN AND PHOSPHORUS BALANCE

Meldolesi,[47] in a study of 48 cases of progressive muscular dystrophy, reported decreased urinary excretion of nitrogen, a delay in the secretion of lipase, diastase and trypsin in the intestine and low concentrations of these enzymes in the intestinal contents. From these observations, he concluded that the disease was the result of dysfunction of the pancreas, with the chief defect an inadequate absorption of protein and a depletion of protein reserves. Milhorat and Toscani,[48] who studied phosphorus, as well as calcium and magnesium, metabolism in 2 patients with progressive muscular dystrophy, were unable to demonstrate any signifi-

38. McCrudden, R. H., and Sargent, C. S.: Hypoglycemia and Progressive Muscular Distrophy, Arch. Int. Med. **17**:465 (April) 1916.

39. Byard, D. S.: Four Cases of Muscular Dystrophy, Internat. Clin. **1**:174, 1923.

40. Brock, S., and Kay, W. E.: A Study of Unusual Endocrine Disturbances: Their Associated Myopathies, Endocrine Balance and Metabolism Findings, Arch. Int. Med. **27**:1 (Jan.) 1921.

41. McCrudden, F. H.: The Nature of the Pathologic Process in Progressive Muscular Dystrophy, Arch. Int. Med. **21**:256 (Feb.) 1918.

42. Magee, M. C. M.: Creatine and Creatinine Metabolism in Progressive Muscular Dystrophy, Am. J. Dis. Child. **43**:19 (Jan.) 1932.

43. Scheman, L.; Lewin, P., and Soskin, S.: Pseudohypertrophic Muscular Dystrophy: An Evaluation of Recent Studies, J. A. M. A. **111**:2265 (Dec. 17) 1938.

44. Elkington, J. St. C., and Goldblatt, M. W.: Effect of Adrenaline in Certain Muscular Disorders, Lancet **2**:693 (Sept. 23) 1933.

45. Miller, B. F., and Van Slyke, D. D.: A Direct Microtitration Method for Blood Sugar, J. Biol. Chem. **114**:583 (July) 1936.

46. Crawford, T.: A Standard Intravenous Glucose Tolerance Test, Arch. Dis. Childhood **13**:69 (March) 1938.

47. Meldolesi, G.: Sulla terapia della distrofia muscolare progressiva a base di estratti pancreatici, Policlinico (sez. prat.) **43**:1187 (June 29) 1936.

48. Milhorat, A. T., and Toscani, V.: Studies in Diseases of Muscle: VIII. Metabolism of Calcium, Phosphorus and Magnesium in Progressive Muscular Dystrophy, Myotonia Atrophica and Familial Periodic Paralysis, Arch. Neurol. & Psychiat. **41**:1130 (June) 1939.

average level of 0.96 mg. per hundred cubic centimeters for the normal subjects. Concentrations of creatinine in the plasma for these two groups were not significantly different. The average level for the dystrophic subjects was 0.72 mg. per hundred cubic centimeters and that for the normal group was 0.77 mg. per hundred cubic centimeters.

CREATINE TOLERANCE

It has been reported that the ability to retain ingested creatine is impaired in patients with progressive muscular dystrophy.[33] Milhorat and Wolff,[34] in a study of 17 dystrophic patients, observed retention of from 12 to 82 per cent of creatine ingested. The lowest retentions were in patients with extensive wasting of the muscles.

Tests for creatine tolerance were made on 5 boys with progressive dystrophy and on 4 normal boys. The subjects were placed for two days on diets which contained no meat, fish, fowl, coffee or tea. On the morning of the second day 1 Gm. of anhydrous creatine was given orally. The urinary output of creatine during the succeeding twenty-four hours was determined and compared with the output of the subjects on a similar diet to which no creatine had been added.

TABLE 6.—*Creatine Tolerance in Normal Subjects and in Patients with Muscular Dystrophy*

Subject	Creatine Retained, %
Normal Children	
J. B.	70.8
S. B.	58.6
R. D.	60.7
L. V.	83.5
Average	68.4
Children with Muscular Dystrophy	
A. T.	75.8
R. R.	63.5
D. W. S.	67.7
R. G.	45.4
J. S.	32.3
Average	56.9

In this manner the percentage of the ingested creatine retained was calculated. The results are shown in table 6.

The normal boys retained from 58.6 to 83.5 per cent of the creatine ingested, with an average retention for the group of 68.4 per cent. The greatest retention in the group of children with progressive muscular dystrophy was 75.8 per cent, while the least amount retained was 32.3 per cent. The average retention for this group was

TABLE 7.—*Basal Metabolic Rates for Patients with Progressive Muscular Dystrophy*

Patient	Sex	Age, Years	Basal Metabolic Rate, %
E. L.	M	19	—14
A. T.	M	10	— 9
M. T.	M	8	—11
C. K.	F	9	—19
R. D. G.	M	11	—16
H. L.	M	51	—19
I. A.	M	35	—18
J. R.	M	9	—15
D. W. S.	M	6	— 4
A. G.	M	8	+ 1
J. S.	M	15	—24
L. G.	M	28	+10
R. A.	M	9	—13
E. M.	M	8	+ 1
Median			—14.5

56.9 per cent. All the patients had an advanced form of the disease, with pronounced and widespread muscular atrophy. However, it was not ascertained that the ability to retain ingested creatine was greatly impaired as compared with the creatine tolerance of normal children.

BASAL METABOLIC RATE

It has been reported by Guarnaschelli-Raggio [35] and by Garot [36] that the basal metabolic rate is increased in patients with progressive muscular dystrophy. The basal metabolic rates were studied for 14 patients of this group. The results are given in table 7 and are expressed as percentages of the normal standards for age and sex according to Boothby and Sandiford.[37] The data represent the average for several determinations on each patient.

33. Gibson, R. B.; Martin, F. T., and Buell, M. V. R.: A Metabolic Study of Progressive Pseudohypertrophic Muscular Dystrophy and Other Muscular Atrophies, Arch. Int. Med. **29**:82 (Jan.) 1922. Harris, M. M., and Brand, E.: Metabolic and Therapeutic Studies in the Myopathies, with Special Reference to Glycine Administration, J. A. M. A. **101**:1047 (Sept. 30) 1933. Milhorat, A. T.: Ueber die Behandlung der progressiven Muskeldystrophie und ähnlicher Muskelerkrankungen mit Glykokoll, Deutsches Arch. f. klin. Med. **174**:487 (Jan. 12) 1933. Levene and Kristeller.[32]

34. Milhorat, A. T., and Wolff, H. G.: Studies in Diseases of Muscle: I. Metabolism of Creatine and Creatinine in Progressive Muscular Dystrophy, Arch. Neurol. & Psychiat. **38**:992 (Nov.) 1937.

35. Guarnaschelli-Raggio, A.: La proteinemia nella distrofia muscolare progressiva primitiva, Arch. per lo stud. d. fisiopat. e clin. d. ricambio **6**:391 (Sept.-Oct.) 1938.

36. Garot, L.: Contribution à l'étude des troubles du métabolisme chimique dans la dénutrition grave du nourrisson: III. Excrétion créatinique et métabolisme basal, Rev. franç. de pédiat. **9**:273, 1933.

37. Boothby, W. M., and Sandiford, I.: Normal Values of Basal or Standard Metabolism: A Modification of the DuBois Standards, Am. J. Physiol. **90**:290 (Nov.) 1929.

produced by progressive muscular dystrophy in the patients of this series were similar to those described by other investigators. It was noted particularly that the original observations of Duchenne,[2] Erb,[3] Landouzy and Dejerine[4] and Gowers[7] were remarkably accurate and complete.

In all of the patients studied the disease was accompanied by increase in creatinuria (in children) or by the appearance of creatine in the urine (in adults). When the rates of excretion of creatine and creatinine for children with progressive muscular dystrophy were com-

of creatine is increased by the feeding of gelatin. Brand and associates[55] obtained a similar and more profound effect from the administration of aminoacetic acid. Neither gelatin nor aminoacetic acid changed the rate of excretion of creatinine, however. Studies of the effect of testosterone propionate on the physiologic creatinuria of childhood and on the creatinuria of muscular dystrophy have been reported on by Hoagland, Shank and Gilder.[56] Evidence was obtained indicating that testosterone brings about retention and storage of creatine in patients with muscular dystrophy. Administra-

TABLE 9.—*Nitrogen Balance in Patients with Muscular Dystrophy* *

Patient	Sex	Age, Years	Weight, Kg.	Nitrogen Intake, Gm.	Feces Nitrogen, Gm.	Urine Nitrogen, Gm.	Total Nitrogen Output, Gm.	Nitrogen Balance, Gm.
D. S.	M	7	25.5	8.00	0.736	6.491	7.227	+0.773
				8.00	0.794	6.072	6.866	+1.134
				8.00	0.742	6.227	6.969	+1.031
				8.00	0.731	6.369	7.100	+0.900
				8.00	0.729	6.074	6.803	+1.197
C. K.	F	9	36.2	11.29	0.513	9.766	10.279	+1.011
				11.29	0.962	9.474	10.436	+0.854
				11.29	0.952	9.007	9.959	+1.331
				11.29	0.926	11.290	12.216	−0.926
				11.29	0.866	9.603	10.469	+0.821
J. R.	M	9	34.0	8.00	0.717	5.748	6.465	+1.535
				8.00	0.693	5.559	6.252	+1.748
				8.00	0.508	6.229	6.737	+1.263
				8.00	0.677	5.871	6.548	+1.452
				8.00	0.602	5.925	6.527	+1.473
G. T.	M	6	24.2	8.00	0.606	6.438	7.044	+0.956
				8.00	0.718	5.936	6.654	+1.346
				8.00	0.607	5.891	6.498	+1.502
				8.00	0.553	6.818	7.371	+0.629
				8.00	0.712	5.902	6.614	+1.386
R. R.	M	4	21.3	10.25	0.764	9.290	10.054	+0.200
				10.24	0.668	8.995	9.663	+0.577
				10.23	0.596	9.474	10.070	+0.161
				9.74	0.615	9.939	10.545	−0.805
				10.25	0.718	9.760	10.478	−0.225
D. W. S.	M	6	21.0	10.21	0.666	9.484	10.150	+0.060
				10.26	0.867	9.046	9.913	+0.345
				10.25	0.621	9.335	9.956	+0.294
				10.25	0.924	9.270	10.194	+0.056
				10.25	0.735	8.383	9.118	+1.132
R. G.	M	8	27.5	13.43	0.966	11.497	12.463	+0.967
				13.44	0.506	9.811	10.317	+3.123
				13.44	1.154	10.425	11.579	+1.861
				13.46	1.146	11.546	12.546	+0.911
				13.44	1.777	11.087	12.864	+0.576

* All data given are in terms of grams per day and represent the average intake or output of nitrogen for each balance study period of seven days.

pared with the physiologic rates of excretion for normal children of the same age and sex, it was found that the excretion of creatine was notably increased and the excretion of creatinine was decreased. The amount of creatinine excreted daily by the patients in our series has remained remarkably constant during the months of study, whereas the quantity of creatine excreted has been much more variable.

The creatinuria of muscular dystrophy is modified by the administration of aminoacetic acid or the androgen testosterone. It was shown by Gibson and Martin[54] that excretion

tion of testosterone produced *no significant* change in excretion of creatinine during the period studied.

The metabolic changes that accompany progressive muscular dystrophy are not limited to the changes in excretion of creatine and creatinine. Evidence has been presented to show that the basal metabolic rate is decreased. In late stages of the disease there are increased

54. Gibson, R. B., and Martin, F. T.: Some Observations on Creatine Formation in a Case of Progressive Pseudohypertrophic Muscular Dystrophy, J. Biol. Chem. 49:319 (Dec.) 1921.

55. Brand, E.; Harris, M. M.; Sandberg, M., and Ringer, A. I.: Studies on the Origin of Creatine, Am. J. Physiol. 90:296 (Oct.) 1929.

56. Hoagland, C. L.; Shank, R. E., and Gilder, H.: Effect of Testosterone Propionate and Methyl Testosterone on Creatinuria in Progressive Muscular Dystrophy, Proc. Soc. Exper. Biol. & Med. 55:49 (Jan.) 1944.

cant abnormality. Nevin[49] observed a low concentration of acid-soluble phosphorus in dystrophic muscles but stated that the changes demonstrated were secondary to degeneration of muscle and were not related to defects in mineral metabolism.

In a search for aberrations in nitrogen and phosphorus metabolism in patients with progressive muscular dystrophy, studies of nitrogen and phosphorus balance were made on 7 children with the disease. The patients were maintained on diets providing 3 Gm. of protein, 2 Gm. of fat and 6 Gm. of carbohydrate per kilogram of body weight per day. The urine and feces were collected for seven day periods.

was comparable to the amounts found by Porter[53] to be retained by normal children on a similar intake of protein. The loss of nitrogen in the feces was not excessive, and the urinary excretion of nitrogen was similar in quantity to that of normal children.[53] Therefore, no defect in the metabolism of nitrogen-containing compounds was apparent from these studies of the nitrogen balance. Retention of phosphorus was observed in all the patients studied. This indicates that no gross abnormality in phosphorus metabolism is associated with progressive muscular dystrophy, an observation which is in agreement with the earlier report of Milhorat and Toscani.[48]

TABLE 8.—*Results of the Intravenous Dextrose Tolerance Test for Normal Subjects and for Patients with Muscular Dystrophy*

				Blood Sugar Concentration, Mg./100 Cc.						
Subject	Sex	Age, Years	Fasting	5 Min.	15 Min.	30 Min.	45 Min.	60 Min.	75 Min.	90 Min.
				Normal Subjects						
W. S.	M	9	88	231	189	154	128	105	90	74
S. B.	M	11	87	270	177	95	84	78	76	74
L. V.	M	11	89	241	194	147	115	96	92	87
J. B.	M	9	75	278	196	123	91	80	78	76
R. D.	M	12	88	235	194	154	133	98	89	80
Average			85.4	250.6	190	134	110.2	91.4	85	78.4
				Patients with Muscular Dystrophy						
A. T.	M	11	78	199	179	119	98	80	72	70
G. T.	M	7	76	210	186	163	141	110	73	70
O. K.	F	9	84	281	217	185	165	107	100	95
I. A.	M	35	55	256	238	195	169	125	90	75
R. B.	M	6	73	195	132	68	60	71	71	44
D. W. S.	M	7	71	243	171	140	116	89	72	66
R. R.	M	5	88	251	256	182	128	104	99	85
R. G.	M	8	70	177	147	113	87	76	71	70
A. G.	M	8	95	207	172	136	124	108	93	77
Average			76.4	224.3	189	144.6	121	96.7	82.3	72.4

The macromethod of Kjeldahl[50] was used for the determination of nitrogen in the urine and the feces. The phosphorus content was determined by a modification of the method of Fiske and Subbarow.[51] The results are recorded in tables 9 and 10. The data given represent the average daily outputs and balances for the seven day periods.

Although the nitrogen content of the diets of these children was somewhat less than the usually accepted requirement for growing children,[52] the patients were maintained in positive nitrogen balance. The quantity of nitrogen retained

COMMENT

A study of a primary degenerative disease of muscle, progressive muscular dystrophy, has been initiated at the Hospital of the Rockefeller Institute for Medical Research, with a series of 40 patients. The majority of the patients had onset of the disease in early childhood, with initial involvement of the muscles of the lower extremities. When the onset was delayed until late childhood or early adult life, the first muscles involved were frequently those of the scapulohumeral group. It was possible to demonstrate genetic influences for 14 of the 40 patients. There were examples of dominant, sex-linked and simple recessive types of inheritance. Both pseudohypertrophy and atrophy existed in affected muscles, with pseudohypertrophy most frequent in the large bulky muscles of the younger patients. The defects

49. Nevin, S.: A Study of the Muscle Chemistry in Myasthenia Gravis, Pseudohypertrophic Muscular Dystrophy and Myotonia, Brain **57**:239 (Oct.) 1934.

50. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry: II. Methods, Baltimore, Williams & Wilkins Company, 1932, p. 516.

51. Fiske, C. H., and Subbarow, Y.: The Colorimetric Determination of Phosphorus, J. Biol. Chem. **66**:375 (Dec.) 1925.

52. Holt, L. E., and Fales, H. L.: The Food Requirements of Children: II. Protein Requirement, Am. J. Dis. Child. **22**:371 (Oct.) 1921.

53. Porter, T.: Metabolism of Normal Pre-School Children: III. Variations in Nitrogen Storage on Constant Diets, J. Am. Dietet. A. **15**:427 (June-July) 1939.

hereditary nature of the disease. Fourteen of the 40 patients were from families in which other cases of the disease had occurred.

The early onset of the disease was demonstrated, the first symptoms having been noted by 62 per cent of this series of patients before the age of 10 years.

The course of progressive muscular dystrophy was most rapid in patients with onset of the disease before the fifth year of life.

There were characteristic changes in the roentgenograms of patients with progressive muscular dystrophy. These alterations include conspicuous streaking of the soft tissue shadows of affected muscle, delayed appearance of centers of ossification in the bones of the hands and in the epiphyses of the long bones and demineralization of other bony structures.

The rate of excretion of creatine was greater and the rate of excretion of creatinine was less in boys with muscular dystrophy than in normal boys of the same age group who were maintained on diets of identical composition. These differences were increased when the subjects were fasting.

The concentration of creatine in the plasma of dystrophic children was greater than the concentration in the plasma of normal subjects. Levels of creatinine in the plasma were unchanged.

The creatine tolerance of children with progressive muscular dystrophy was not significantly different from that of normal children of the same age group.

The basal metabolic rate was low in children with the disease. The median basal metabolic rate for a group of 14 patients was —14.5 per cent of normal standards.

The fasting level of the blood sugar and the response to intravenous administration of dextrose were essentially the same in dystrophic patients as in normal subjects. One patient with muscular dystrophy gave evidence of an increased rate of utilization of dextrose injected intravenously.

Patients with progressive muscular dystrophy were in positive nitrogen and phosphorus balance.

deposits of subcutaneous fat and infiltration of muscle by fat and connective tissue. In roentgenograms of patients with the disease there are evidences of abnormality in the calcifying process of bone, as shown by the frequent occurrence of delayed ossification of the bones of the hands and the epiphyses of the long bones and by demineralization of other bony structures. There is, however, no evidence of abnormality in dextose tolerance or in nitrogen or phosphorus balance. Undoubtedly, specific meta-

vitamin E [58] and pyridoxine,[59] have been proposed for progressive muscular dystrophy. Each of these methods has, after thorough trial, proved singularly ineffective. Any rational approach to the successful treatment of the disease depends on more specific information concerning its nature and the metabolic changes effected by it.

SUMMARY

A clinical study of 40 patients with progressive muscular dystrophy gave evidence of the

TABLE 10.—*Phosphorus Balance in Patients with Muscular Dystrophy* *

Patient	Sex	Age, Years	Weight, Kg.	Phosphorus Intake, Gm.	Feces Phosphorus, Gm.	Urine Phosphorus, Gm.	Total Phosphorus Output, Gm.	Phosphorus Balance, Gm.
D. S.	M	7	25.5	0.920	0.329	0.549	0.878	+0.042
				0.935	0.329	0.489	0.818	+0.117
				0.935	0.284	0.557	0.841	+0.094
				0.935	0.293	· 0.574	0.867	+0 068
				0.935	0.283	0.466	0.749	+0.168
C. K.	F	9	36.2	1.023	0.329	0.595	0.924	+0.099
				1.023	0.460	0.591	1.051	—0.028
				0.999	0.220	0.625	0.845	+0.154
				1.010	0.321	0.746	1.067	—0.057
				1.033	0.315	0.655	0.970	+0.063
J. R.	M	9	34.0	0.941	0.322	0.388	0.710	+0.231
				0.941	0.276	0.504	0.780	+0.161
				0.948	0.335	0.509	0.844	+0.104
				0.942	0.321	0.509	0.830	+0.112
				0.941	0.256	0.518	0.774	+0.167
G. T.	M	6	24.2	0.941	0.268	0.564	0.832	+0.109
				0.941	0.361	0.401	0.762	+0.179
				0.941	0.274	0.509	0.783	+0.158
				0.928	0.202	0.562	0.764	+0.164
				0.928	0.301	0.452	0.753	+0.175
R. R.	M	4	21.3	1.296	0.531	0.810	1.341	—0.045
				1.280	0.453	0.727	1.180	+0.100
				1.293	0.449	0.675	1.124	+0.169
				1.228	0.500	0.759	1.259	—0.031
				1.306	0.531	0.742	1.273	+0.033
D. W. S.	M	6	21.0	1.280	0.502	0.656	1.158	+0.122
				1.257	0.488	0.651	1.139	+0.118
				1.278	0.539	0.613	1.152	+0.126
				1.278	0.595	0.629	1.224	+0.054
				1.268	0.529	0.685	1.214	+0.054
R. G.	M	8	27.5	1.518	0.588	0.719	1.307	+0.274
				1.609	0.642	0.642	1.536	+0.073
				1.608	0.802	0.599	1.402	+0.206
				1.609	0.845	0.715	1.570	+0 039
				1.602	0.888	0.688	1.576	+0.086

* All data given are in terms of grams per day and represent the average intake or output of phosphorus for each balance study period of seven days.

bolic changes occur in the affected musculature, but these have not as yet been discovered or clarified. Investigations concerned with various processes and stages of intermediary muscle metabolism in progressive muscular dystrophy are under way in this laboratory and will be reported on subsequently.

Within recent years various types of therapy, including treatment with aminoacetic acid,[57]

57. Braestrup, P. W.: The Action of Glycine (Glycocoll) on Muscular Dystrophy and Other Diseases, Acta med. Scandinav. **89**:231, 1936. Mettel, H. B.: Pseudohypertrophic Muscular Dystrophy: Further Observations of the Therapeutic Effects of Glycine and Other Substances Used in the Treatment of Fourteen Cases of Muscular Dystrophy, J. Pediat. **5**:359 (Sept.) 1934.

58. (a) Harris, M. M.: Negative Therapeutic and Metabolic Effects of Synthetic Alpha-Tocopherol (Vitamin E) in Muscular Dystrophy, Am. J. M. Sc. **202**:258 (Aug.) 1941. (b) Viets, H. R.; Trowbridge, E. H., and Gunderson, T. E.: The Treatment of Certain Muscular Atrophies with Vitamin E, with a Note on Diagnosis and the Electromyograms, ibid. **203**:558 (April) 1942. (c) McBryde, A., and Baker, L. D.: Vitamin Therapy in Progressive Muscular Dystrophy, J. Pediat. **18**:727 (June) 1941. (d) Lubin, A. J.: Use of Alpha Tocopherol in the Treatment of Neuromuscular Disorders, Arch. Int. Med. **69**:836 (May) 1942. (e) Hawke, W. A.: Vitamin Therapy of Muscular Dystrophy, Canad. M. A. J. **47**:153 (Aug.) 1942. (f) Ferrebee, J. W.; Klingman, W. O., and Frantz, A. M.: Vitamin E and Vitamin B6: Clinical Experience in the Treatment of Muscular Dystrophy and Amyotrophic Lateral Sclerosis, J. A. M. A. **116**:1895 (April 26) 1941.

59. McBryde and Baker.[58c] Hawke.[58e] Ferrebee and associates.[58f]

Creutzfeld [14] and Jakob [15] concluded that the process was inflammatory, basing their conclusion partly on the presence of a perivascular infiltration of hematogenous elements and partly on the presence of the triad of degeneration, proliferation and exudation. Other authors, such as Weimann,[16] Anton and Wohlwill,[17] Walter [18] and Guttmann,[19] stated that the perivascular infiltration, if not pronounced, was an expression of a secondary reaction to the breakdown of the nerve parenchyma: "symptomatic inflammation."

In the presence of such opposing opinions, Bouman [3] concluded that the nature of the pathologic process in diffuse sclerosis, whether inflammatory or degenerative, is as yet undecided. It is disconcerting that in the two important conditions with patchy and diffuse demyelination neuropathologists of experience are unable to agree on the interpretation of the histopathologic process.

Demyelinating Encephalomyelitides.—A similar controversy exists concerning the interpretation of the histopathologic changes in the acute encephalomyelitides following vaccination or infectious diseases, ·such as measles, chickenpox, scarlet fever and influenza. Here also, while one group of investigators is convinced of the typical inflammatory nature of the pathologic process, another is hesitant in the definition and speaks of an encephalopathy or of an inflammatory process with special characteristics.

The controversy has also extended into the field of so-called acute multiple sclerosis. Of course, for investigators who deny the inflammatory nature of the pathologic process of multiple sclerosis there is no room for an acute inflammatory stage of that disease, whereas the acceptance of an acute inflammatory process in the acute phase of the disease becomes easier for those who believe in the inflammatory nature

of multiple sclerosis and regard the full blown disease as its chronic stage. The same variations of opinion are encountered in the literature concerned with the interpretation of so-called Devic's disease, or acute optic neuroencephalomyelopathy. Although many authors have stated that this condition is a clinicopathologic entity, others have claimed that it is an acute encephalomyelitis, akin to acute multiple sclerosis. Marinesco, Draganesco, Sager and Grigoresco [20] stated that there are transitory stages between ophthalmoneuromyelitis and diffuse sclerosis. Here, also, one finds conflicting reports and interpretations as to the nature of the histopathologic process. To mention the reports of only a few authors, while in Beck's [21] cases lymphocytic and leukocytic infiltration was dominant, in the case of Guillain, Alajouanine, Bertrand and Garcin [22] the process was concluded to be degenerative.

The question has been raised why in the presence of different etiologic agents the cerebral pathologic changes in the encephalitides following various infectious diseases are fundamentally the same. How can one reconcile the fact that after vaccination against smallpox or rabies pathologic changes in the brain are identical with those following measles, scarlet fever or chickenpox, in which different viruses, or even a streptococcus, may be at work? Yet Bassoe and Grinker [23] asserted that the cerebral changes of encephalomyelitis due to rabies vaccine were identical with the changes following the use of cowpox vaccine or an attack of smallpox or measles. In their case of encephalomyelitis following subcutaneous injection of fourteen doses of 2 cc. of the rabies (Pasteur) vaccine, the changes were striking in the spinal cord, where lymphocytes and gitter cells were observed about the blood vessels in areas corresponding chiefly to the patches of demyelination. Since the encephalomyelitis following use of rabies vaccine and cowpox vaccine resembles nonvaccinal encephalomyelitis associated with smallpox, measles and other virus diseases, it is likely, they concluded, "that we are dealing with an inflammatory disease caused by an attenuated virus."

14. Siemerling, E., and Creutzfeld, H.: Bronzekrankheit und sklerosierende Encephalomyelitis, Arch. f. Psychiat. 68:217, 1923.

15. Jakob, A.: Zur Pathologie der diffusen infiltrativen Encephalomyelitis in ihren Beziehungen zur diffusen und multiplen Sklerose, Ztschr. f. d. ges. Neurol. u. Psychiat. 27:290, 1915.

16. Weimann, W.: Zur Kenntnis der sogennanten diffusen Hirnsklerose, Ztschr. f. d. ges. Neurol. u. Psychiat. 104:411, 1926.

17. Anton, G., and Wohlwill, F.: Multiple nichteitrige Encephalomyelitis und multiple Sklerose, Ztschr. f. d. ges. Neurol. u. Psychiat. 12:31, 1912.

18. Walter, F. K.: Zur Symptomatologie und Anatomie der diffusen Hirnsklerose, Monatschr. f. Psychiat. u. Neurol. 94:87, 1918.

19. Guttmann, E.: Zur Kasuistik der "sklerosierenden Encephalitis," Ztschr. f. d. ges. Neurol. u. Psychiat. 94:62, 1925.

20. Marinesco, G.; Draganesco, S.; Sager, O., and Grigoresco, D.: Sur une forme particulière anatomoclinique d'opthalmo-neuromyélite, Rev. neurol. 2:193. 1930.

21. Beck, G.: A Case of Diffuse Myelitis Associated with Optic Neuritis, Brain 50:687, 1927.

22. Guillain, G.; Alajouanine, T.; Bertrand, I., and Garcin, R.: Sur une forme anatomo-clinique spéciale de neuromyélite optique nécrotique aïgue, Ann. de méd. 24:24, 1928.

23. Bassoe, P., and Grinker, R. R.: Human Rabies and Rabies Vaccine Encephalomyelitis, Arch. Neurol. & Psychiat. 23:1138 (June) 1930.

PATHOLOGY OF DEMYELINATING DISEASES AS AN ALLERGIC REACTION OF THE BRAIN

A. FERRARO, M.D.

NEW YORK

An important controversial issue is the interpretation of the pathology of primary demyelinating processes of the central nervous system. Neuropathologists have had considerable difficulty in agreeing on the significance of the vascular and perivascular reactions often observed with demyelinating diseases of the central nervous system. One group of investigators speaks of such conditions as degenerative and another as inflammatory. A conciliatory attitude is taken by workers who claim that the perivascular reaction is the expression of so-called symptomatic inflammation, a local reaction to disintegrated material. This controversy has run its gamut in the evaluation and interpretation of multiple sclerosis, diffuse sclerosis and the demyelinating encephalomyelitides following vaccination and infectious diseases, such as measles, scarlet fever, influenza and rabies.

PATHOGENESIS

Multiple Sclerosis.—One needs only cite Hassin's[1] opinion that this disease is degenerative and that the perivascular reaction is formed mainly, if not exclusively, of gitter cells. Lymphocytes, according to this author, may be present, but in very small numbers, and in the majority of cases are absent altogether. The lymphocytes when present denote a reaction against invasion of foreign substances from the parenchyma, such as gitter cells. Hassin stated the opinion that there would be no grounds for designating multiple sclerosis as an inflammatory process because of the occasional presence of a few lymphocytes and for ignoring the immense phenomena of degeneration.

Conversely, Steiner[2] was positive in the statement that multiple sclerosis is an inflammatory disease and that perivascular infiltration of lymphocytes and plasma cells is a common feature, especially in the acute stage or in the stage of reactivation of a chronic process. In cases of a protracted course a mixture of lymphocytes and compound granular corpuscles surrounds the blood vessels.

"Diffuse Sclerosis."—One may conclude from Bouman's[3] monograph that the pathologic process in this disease, like that of multiple sclerosis, is regarded as degenerative by one group of authors and as inflammatory by another. Marie and Foix,[4] Kraus and Weil,[5] Hermel,[6] Bouman[3] (case 1), Globus and Strauss[7] and Davison and Schick[8] stated that in sporadic cases the process is degenerative. In cases of the familial form, such as those described by Scholz,[9] the pathologic process was asserted to be essentially degenerative. Conversely, Schilder,[10] Bielschowsky and Henneberg,[11] Kufs,[12] Neubürger,[13] Siemerling and

From the Department of Neuropathology, New York State Psychiatric Institute and Hospital.

1. Hassin, G.: Histopathology of the Peripheral and Central Nervous System, New York, Paul B. Hoeber, Inc., 1940.

2. Steiner, G.: Multiple und diffuse Sklerose, in Bumke, O.: Handbuch der Geisteskrankheiten, Berlin, Julius Springer, 1930, vol. 11, p. 289.

3. Bouman, L.: Diffuse Sclerosis, Bristol, England, John Wright & Sons, Ltd., 1934.

4. Marie, P., and Foix, C.: Sclérose intracérébrale et symmetrique, Rev. neurol. 27:1, 1914.

5. Kraus, W. M., and Weil, A.: An Unusual and Protracted Case of Schilder's Disease, J. Nerv. & Ment. Dis. 62:620, 1925.

6. Hermel, H.: Ueber einen Fall von Encephalo-Myelomalacia chronica diffusa, Deutsche Ztschr. f. Nervenh. 68:338, 1921.

7. Globus, J. H., and Strauss, I.: Progressive Degenerative Subcortical Encephalopathy, Arch. Neurol & Psychiat. 20:1190 (Dec.) 1928.

8. Davison, C., and Schick, W.: Encephalopathia Periaxialis Diffusa, Arch. Neurol. & Psychiat. 25:1063 (May) 1931.

9. Scholz, W.: Klinische pathologisch-anatomische und erbbiologische Untersuchungen bei familiärer diffuser Hirnsklerose im Kindesalter, Ztschr. f. d. ges. Neurol. u. Psychiat. 99:651, 1925.

10. Schilder, P.: Zur Kenntnis der sogenannten diffusen Sclerose (Ueber Encephalitis periaxialis diffusa), Ztschr. f. d. ges. Neurol. u. Psychiat. 10:1, 1912.

11. Bielschowsky, M., and Henneberg, R.: Ueber familiäre diffuse Sklerose (Leukodystrophia cerebri progressiva hereditaria), J. f. Psychol. u. Neurol. 33:12, 1927.

12. Kufs, H.: Ein bemerkenswerter Uebergangsfall von diffusen zu multiplen Hirnsklerose, Arch. f. Psychiat. 93:564, 1931.

13. Neubürger, K.: Histologisches zur Frage der diffusen Hirnsklerose, Ztschr. f. d. ges. Neurol. u. Psychiat. 73:336, 1921.

origin, based on Chevassut's work and supported by the investigations of Purves-Stewart[35] (Spherula insularis), is discredited, as is the theory of the spirochetal origin of the process (Spirochaeta argentinensis), as advocated by Kuhn and Steiner.[36]

Toxic Origin.—The toxic origin of the disease (toxemia in the general sense) was advocated by Hallervorden and Spatz.[37] More specifically, lead (Cone, Russel and Harwood[38]), arsenic (Ecker and Kernohan[39]) and carbon monoxide (Hilpert[40]) have been mentioned as causation factors. Experimentally, tetanus toxin (Claude[41]; Putnam, McKenna and Evans[42]), saponin, sodium taurocholate, streptolysin (Weil[43]), carbon monoxide (Putnam and associates[44]), potassium cyanide (Ferraro[45], Rubino,[46] Hurst[47]), vinilamin (Luzzatto and Levi[48]), sulfanilamide (Fisher[49]) and cultures of Aspergillus fumigatus (Ceni and Besta[50]) have been considered as etiologic agents.

Lipolytic Theory.—Studies of lipolytic origin, initiated by Marburg,[51] have been followed, with variations, by Quinan,[52] Brickner,[53] Crandall and Cherry,[54] Altmann and Goldhammer[55] and Weil and Cleveland.[56] The presence of myelinolytic substance has been reported by Weil and Luhan[57] in the urine of patients with disseminated sclerosis.

Theory of Vascular Obstruction.—This theory has been developed to a considerable extent by Putnam[58] and his co-workers McKenna, Morrison and Alexander,[59] who predicated the occurrence of vascular thrombi as the cause of the parenchymatous changes. Experimentally, Putnam[60] and co-workers (Hoefer and Gray[61]) were able to reproduce encephalitis and sclerotic plaques with intravenous injections of oil or various coagulants.

Allergic Theory.—This theory, which has been mentioned clinically by various authors, but never interpreted satisfactorily from the pathologic standpoint, seems to have developed from various sources. Reports already exist in

35. Purves-Stewart, J.: Disseminated Sclerosis: Experimental Vaccine Treatment, Lancet **1**:440, 1930.

36. Kuhn, P., and Steiner, G.: Ueber die Ursache der multiplen Sklerose, Ztschr. f. Hyg. u. Infektionskr. **90**:417, 1920.

37. Hallervorden, T., and Spatz, H.: Ueber die konzentrische Sklerose und die physikalisch-chemischen Faktoren bei der Ausbreitung von Entmarkungsprocessen, Arch. f. Psychiat. **98**:641, 1935.

38. Cone, W.; Russel, C., and Harwood, R. U.: Lead as a Possible Cause of Multiple Sclerosis, Arch. Neurol. & Psychiat. **31**:236 (Feb.) 1934.

39. Ecker, A. D., and Kernohan, J. W.: Arsenic as a Possible Cause of Subacute Encephalomyelitis, Arch. Neurol. & Psychiat. **45**:24 (Jan.) 1941.

40. Hilpert, P.: Kohlenoxydvergiftung und multiple Sklerose, Arch. f. Psychiat. **89**:117, 1929.

41. Claude, H.: Myelite éxperimentale sub-aiguë par intoxication tetanique, J. de physiol. et de path. gén. **29**:843, 1897.

42. Putnam, T. J.; McKenna, T. B., and Evans, J.: Experimental Multiple Sclerosis in Dogs from Injection of Tetanus Toxin, J. f. Psychol. u. Neurol. **44**:460, 1932.

43. Weil, A.: The Effect of Hemolytic Toxins on Nervous Tissue, Arch. Path. **9**:828 (April) 1930.

44. Putnam, T.; Morrison, L., ·and McKenna, J.: Experimental Demyelination, Tr. Am. Neurol. A. **57**:451, 1931.

45. Ferraro, A.: Experimental Toxic Encephalomyelopathy, Psychiatric Quart. **7**:267, 1933.

46. Rubino, A.: Alterazioni della mielina da tossici, Riv. di pat. nerv. **45**:191, 1935.

47. Hurst, W.: Experimental Demyelination of the Central Nervous System, Australian J. Exper. Biol. & M. Sc. **120**:297, 1942.

48. Luzzatto, R., and Levi, A.: L'action de la vinilamin sur le système nerveux, Arch. internat. de pharmacodyn. et de therap. **26**:5, 1922.

49. Fisher, J. H.: Encephalomyelitis Following Administration of Sulphanilamide, Lancet **2**:301, 1939.

50. Ceni, C., and Besta, C.: Sclerosi in placche sperimentale da tossici aspergillari, Riv. sper. di freniat. **31**:125, 1905.

51. Marburg, O.: Die sogennante akute multiple Sklerose, Jahrb. f. Psychiat. **27**:211, 1906.

52. Quinan, C.: On Regional Lipolytic Activity in the Normal Human Brain, J. M. Research **35**:79, 1916.

53. Brickner, R. M.: Studies on the Pathogenesis of Multiple Sclerosis, Arch. Neurol. & Psychiat. **23**:715 (April) 1930; Recent Experimental Work on the Pathogenesis of Multiple Sclerosis, J. A. M. A. **106**:2117 (June 20) 1936.

54. Crandall, L. A., Jr., and Cherry, I. S.: Blood Lipase, Diastase and Esterase in Multiple Sclerosis, Arch. Neurol. & Psychiat. **27**:367 (Feb.) 1932.

55. Altmann, O., and Goldhammer, H.: Lipase und Cholesterinbestimmungen bei der multiplen Sklerose, Klin. Wchnschr. **2**:1017, 1937.

56. Weil, A., and Cleveland, D. A.: A Serologic Study of Multiple Sclerosis, Arch. Neurol. & Psychiat. **27**:375 (Feb.) 1932.

57. Weil, A., and Luhan, J. A.: The Demonstration of Myelolytic Substances in the Urine of Patients with Disseminated Sclerosis, Arch. Neurol. & Psychiat. **34**:459 (Aug.) 1935.

58. Putnam, T. J.: Evidences of Vascular Occlusion in Multiple Sclerosis and "Encephalomyelitis," Arch. Neurol. & Psychiat. **37**:1298 (June) 1937.

59. (*a*) Putnam, T. J.; McKenna, J. B., and Morrison, L. R.: Studies in Multiple Sclerosis: The Histogenesis of Experimental Sclerotic Plaques and Their Relation to Multiple Sclerosis, J. A. M. A. **97**:1591 (Nov. 28) 1931. (*b*) Putnam, T. J., and Alexander, L.: Disseminated Encephalomyelitis: A Histologic Syndrome Associated with Thrombosis of Small Cerebral Vessels, Arch. Neurol. & Psychiat. **41**:1087 (June) 1939.

60. Putnam, T. J.: Studies in Multiple Sclerosis: "Encephalitis" and Sclerotic Plaques Produced by Venular Obstruction, Arch. Neurol. & Psychiat. **33**:929 (May) 1935.

61. Hoefer, P. F. A.; Putnam, T. J., and Gray, M. G.: Experimental "Encephalitis" Produced by Intravenous Injection of Various Coagulants, Arch. Neurol. & Psychiat. **39**:799 (April) 1938.

The possibility that encephalitis following vaccination results from an activated virus has been considered, and recently Milligan and Neubürger,[24] reporting on the pathologic changes of postvaccinal encephalitis in adults, emphasized the negative aspect of their bacteriologic investigation.

This difficulty in reconciling the similarity of the pathologic process with the action of various etiopathogenic agents is reflected in the perplexity expressed by Winkelman,[25] when, in order to explain the pathologic features of cerebral complications following scarlet fever, he resorted to the hypothesis that the streptococcus releases a virus dormant in the central nervous system, and added that "unless the same virus is released in the other acute exanthematic infectious processes . . . it is impossible to correlate the whole group."

From this brief review one can conclude that confusion exists not only in the evaluation of the pathologic process of multiple and of diffuse sclerosis, the cause of which is still a baffling problem, but in the interpretation of identical changes in the central nervous system developing in the course of diseases the etiologic factor of which is better known.

Interest and speculation have been stimulated concerning the possibility that there is, as the basis of these various processes, a common factor, a common denominator, the action of which may result in similarities in the pathologic reactions of the brain.

A detailed study of histopathologic data obtained from my own material and from material reported in the literature has gradually led me to believe that a common ground for evaluation of the pathologic changes of the central nervous system in this large and apparently varied group of diseases could be found by viewing the histologic picture as an allergic reaction.

Clinically it is suggested in the literature that some of the acute encephalomyelitides may be considered as allergic manifestations. This clinical attempt to regard allergy as the etiologic factor in demyelinating diseases has extended to both the chronic and the acute demyelinating processes. Glanzmann[26] gave various arguments in favor of the interpretation of the nervous complications of chickenpox, smallpox and vaccination as

anaphylactic reactions. Van Bogaert[27] asserted that the nervous sequelae of vaccination were the expression of a hyperallergic reaction of the nervous system resulting from insufficiency of the "cutaneous pexic functions" (Dujardin). Finley,[28] in a discussion of the pathogenesis of encephalitis occurring with vaccination, smallpox and measles, offered clinical evidence that the response of the brain, like that of other tissues or organs of the body, is allergic and that the period of incubation of the encephalitis corresponds to the period of the particular exanthem with which it occurs. He stated that as yet little is understood of the reactions of hypersensitivity and immunity in the brain. Kennedy[29] stated that the clinical events of multiple sclerosis resemble the events of localized allergic edema of the central nervous system. Reese[30] also advocated study of these diseases from the standpoint of allergy. Pardee,[31] Rowe[32] and Winkelman and Moore[33] reported clinical cases of nervous manifestations which they related to allergic reaction of the nervous system; Marburg,[34] in referring to the Shwartzman phenomenon of local tissue reactivity, expressed the opinion that a similar mechanism may exist in multiple sclerosis.

The same uncertainties existing in the clinical and pathologic interpretation of demyelinating disease are encountered with respect to their causation, as is evident from a brief review of the etiologic theories advanced.

ETIOLOGIC THEORIES

Infectious Origin.—For multiple sclerosis and diffuse sclerosis, the theory of an infectious

24. Milligan, R. M., and Neubürger, K.: Postvaccinal Encephalitis in Adults, J. Neuropath. & Exper. Neurol. **1**:416, 1942.

25. Winkelman, N. W.: Scarlatinal Encephalomyelitis, J. Neuropath. & Exper. Neurol. **1**:363, 1942.

26. Glanzmann, E.: Die nervösen Komplikationen der Varizellen, Variola und Vakzine, Schweiz. med. Wchnschr. **57**:145, 1927.

27. van Bogaert, L.: Essai d'interpretation des manifestations nerveuses observées au cours de la vaccination de la maladie sérique et des maladies éruptives, Rev. neurol. **2**:1, 1932.

28. Finley, K. H.: Pathogenesis of Encephalitis Occurring with Vaccination, Variola and Measles, Arch. Neurol. & Psychiat. **39**:1047 (May) 1938.

29. Kennedy, F.: Allergy and Its Effects on the Central Nervous System, J. Nerv. & Ment. Dis. **88**: 91, 1938.

30. Reese, H. H.: Multiple Sclerosis, in Reese, H. H.; Lewis, N. D. C., and Sevringhaus, E. L.: The Year Book of Neurology, Psychiatry and Endocrinology, Chicago, The Year Book Publishers, Inc., 1942, p. 180.

31. Pardee, I.: Allergic Reactions in the Central Nervous System: Report of Two Cases, Arch. Neurol. & Psychiat. **39**:1360 (June) 1938.

32. Rowe, A. H.: Clinical Allergy in the Nervous System, J. Nerv. & Ment. Dis. **99**:854, 1944.

33. Winkelman, N. W., and Moore, M. T.: Allergy and Nervous Diseases, J. Nerv. & Ment. Dis. **93**:736, 1941.

34. Marburg, O.: New Studies in Multiple Sclerosis: Paraencephalomyelitis Periaxialis Scleroticans, J. Mt. Sinai Hosp. **9**:640, 1942.

the literature of the precipitation of encephalomyelitis, myelitis and multiple sclerosis by the administration of serums and vaccines (Gayle and Bowen,[62] Winkelman and Gotten[63]) or in the course of the Pasteur treatment for rabies (Wilson,[64] Bassoe and Grinker,[23] Scheinker[65]). In addition, demyelination of the central nervous system of monkeys has been produced experimentally after intramuscular injection of aqueous emulsions and of the alcohol-ether extract of normal rabbit brain (Rivers, Sprunt and Berry[66]; Rivers and Schwentker[67]; Ferraro and Jervis[68]). Then, again, the experimental production of anaphylactic lesions in the central nervous system of guinea pigs and rabbits (Davidoff, Seegal and Seegal[69]; Alexander and Campbell[70]; Abell and Schenck[71]) and of monkeys (Kopeloff, Davidoff and Kopeloff[72]; Jervis, Ferraro and the Kopeloffs[73]) should be noted. Jervis[74] after injecting aqueous extract of guinea pig kidney in rabbits obtained antibodies which when injected in the carotid artery of rabbits resulted in areas of cerebral

demyelination. Recently I[75] described the pathologic picture in 2 cases of encephalitis following scarlet fever; from the study of the vascular reaction, I concluded that the pathologic process in these cases was the expression of a hyperergic reaction.

Nevertheless, no discussion is to be found in the literature of the evaluation and interpretation of the pathologic process of demyelinating diseases in the human brain in the light of an allergic reaction. Is there in the neuropathologic features of demyelinating processes any analogy to or identity with the pathologic features described in the brain or in other organs in experimental allergic states?

PATHOLOGIC FEATURES OF DEMYELINATING DISEASES

The fundamental pathologic features of multiple and diffuse sclerosis may first be analyzed. It is accepted that the severity and the distribution of the lesions are likely to vary from one case to another. I shall not describe the important features of demyelination, the involvement of axis-cylinders and the glial reaction. No disagreement seems to exist with respect to the variability in the extension and intensity of the loss of myelin sheaths. Slightly more controversial is the question of the intensity of involvement of the axis-cylinders. Although considerable variation has been reported, no substantial disagreement seems to exist on this point. Universally accepted, also, is the glial reaction. Of major importance is the controversy of the vascular reaction. In my experience, perivascular exudate is always present in cases of acute disease, and almost always in cases of the less acute or the chronic stage. In most cases the exudate is formed chiefly of lymphocytes and compound granular corpuscles. The lymphocytes at times constitute the bulk of the perivascular exudate (figs. 1 and 2 A). The intensity of the lymphocytic reaction varies from case to case but does not seem to be related to the intensity of the surrounding degenerative process. A lymphocytic reaction is also noted in the meninges (fig. 2 B). Large mononuclear cells, some being round and others having a polygonal, epithelioid appearance, are often present. The size of these cells varies from one case to another, and in certain instances a tendency to fusion of these elements is noticeable. Plasma cells are also noted, being more conspicuous in the very acute stage or in areas in which the pathologic

62. Gayle, R. F., and Bowen, R. H.: Acute Ascending Myelitis Following the Administration of Typhoid Vaccine, J. Nerv. & Ment. Dis. **78**:221, 1933.

63. Winkelman, N. W., and Gotten, N.: Encephalomyelitis Following the Use of Serum and Vaccine, Am. J. Syph. & Neurol. **19**:414, 1935.

64. Wilson, S. A. K.: Neurology, Baltimore, Williams & Wilkins Company, 1940, vol. 1, p. 166.

65. Scheinker, M.: Disseminated Encephalomyelitis and Its Relationship to Multiple Sclerosis, J. Neuropath. & Exper. Neurol. **2**:418, 1943.

66. Rivers, T. M.; Sprunt, D. H., and Berry, G. P.: Observations on Attempts to Produce Acute Disseminated Encephalomyelitis in Monkeys, J. Exper. Med. **58**:39, 1933.

67. Rivers, T. M., and Schwentker, F.: Encephalomyelitis Accompanied by Myelin Destruction Experimentally Produced in Monkeys, J. Exper. Med. **61**:689, 1935.

68. Ferraro, A., and Jervis, G. A.: Experimental Disseminated Encephalopathy in the Monkey, Arch. Neurol. & Psychiat. **43**:195 (Feb.) 1940.

69. Davidoff, L. M.; Seegal, B. C., and Seegal, D.: The Arthus Phenomenon: Local Anaphylactic Inflammation in the Rabbit Brain, J. Exper. Med. **55**:163, 1932.

70. Alexander, L., and Campbell, A. C.: Local Anaphylactic Lesions of the Brain in Guinea Pigs, Am. J. Path. **13**:229, 1937.

71. Abell, R. G., and Schenck, H. P.: Microscopic Observation on the Behavior of Living Blood Vessels of the Rabbit During the Reaction of Anaphylaxis, J. Immunol. **34**:195, 1938.

72. Kopeloff, N.; Davidoff, L. M., and Kopeloff, L.: General and Cerebral Anaphylaxis in the Monkey (Macacus Rhesus), J. Immunol. **30**:6, 1936.

73. Jervis, G. A.; Ferraro, A.; Kopeloff, L. M., and Kopeloff, N.: Neuropathologic Changes Associated with Experimental Anaphylaxis in Monkeys, Arch. Neurol. & Psychiat. **45**:733 (May) 1941.

74. Jervis, G. A.: Forssman's "Carotid Syndrome," Arch. Path. **35**:560 (April) 1943.

75. Ferraro, A.: Allergic Brain Changes in Post-Scarlatinal Encephalitis, J. Neuropath. & Exper. Neurol. **3**:239 (July) 1944.
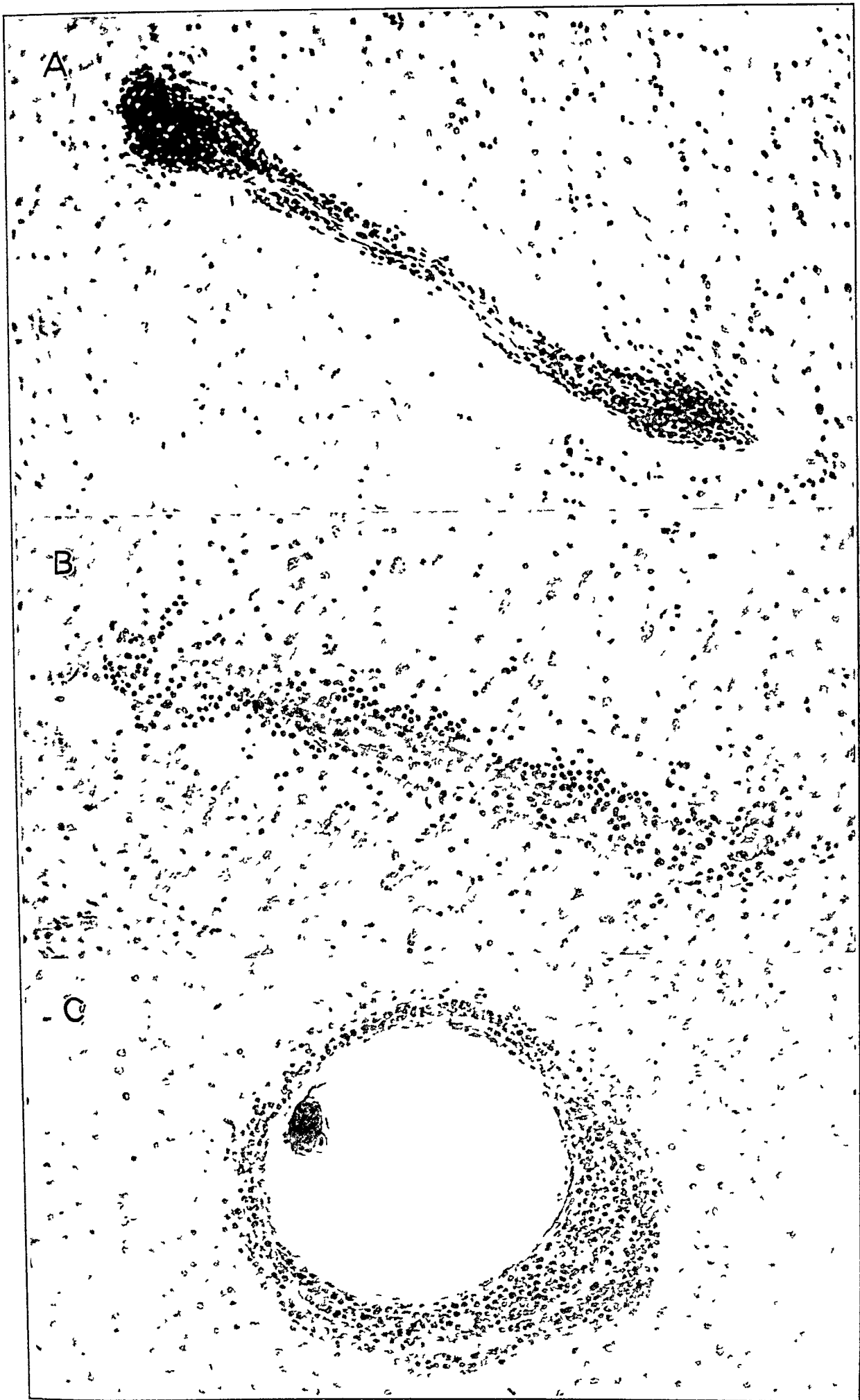
Fig. 1.—Blood vessels surrounded by lymphocytic reactions of various intensities. *A*, Nissl stain; *B* and *C*, hematoxylin and eosin stain.

process is severe. Polymorphonuclear elements, though generally absent, may be encountered both in cases of multiple sclerosis (Putnam [76]) and in cases of diffuse sclerosis (Bouman [3]).

In addition to lymphocytes and large mononuclear cells, a great number of compound granular corpuscles are generally present in the exudate. These cells originate from microglia cells, part of the reticuloendothelial system, and the equivalent of the histiocytes of other organs. All stages of transition between the microglia and histiocytes is noticeable. In such an event the proportion of the two elements varies considerably. At times the compound granular corpuscles are few and are mixed with lymphocytes, which stand out in hematoxylin-eosin preparations (fig. 3). At times the two types of cells occur with equal frequency, and the innermost layers of the perivascular reaction are generally formed of lymphocytes and other hematogenous cells, which may occupy more than one layer of the exudate, and the outer layers of compound
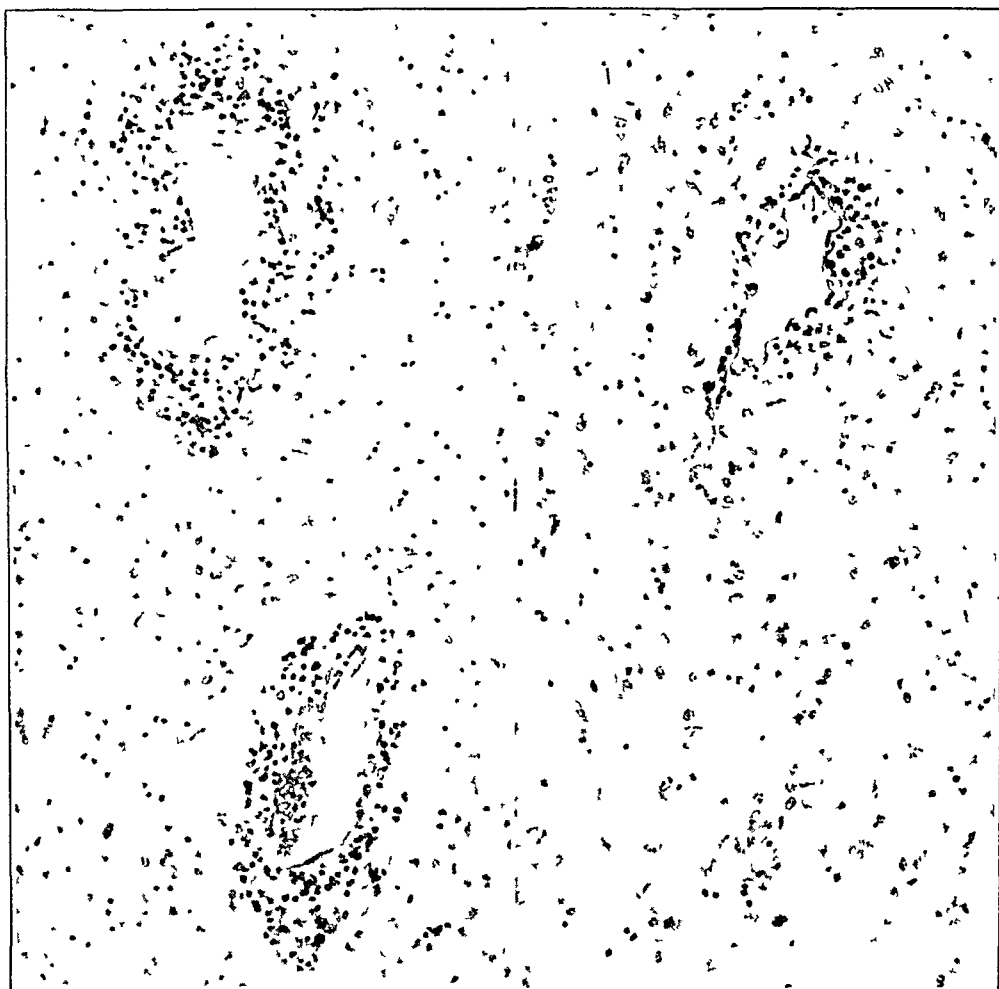
Fig. 3.—Blood vessels surrounded by a mixture of lymphocytes and compound granular corpuscles. Hematoxylin and eosin stain.

cells and the compound granular corpuscles may be encountered. At times the microglia cells are in a state of hypertrophy and, before vacuolation of the cytoplasm, when collected in a mass, give the impression of a mosaic structure, the appearance being analogous to that of a collection of histiocytes in other organs. Free compound granular corpuscles are also seen in the surrounding tissue. Often a combination of lymphocytes

granular corpuscles. Occasionally one pole of the blood vessel may be surrounded by lymphocytes and the other by compound granular corpuscles.

The walls of the blood vessels themselves are more or less involved, and their thickening has been reported, especially in the smaller vessels. Hyaline degeneration is not uncommon. One needs only to refer to the observations of Putnam and Alexander [59b] to appreciate the frequency and importance of thrombus formation.

Necrotic areas may be present, especially in the very acute stage or with reactivation of the

76. Putnam, T. J.: Studies in Multiple Sclerosis: Similarities Between Some Forms of "Encephalomyelitis" and Multiple Sclerosis, Arch. Neurol. & Psychiat 35:1289 (June) 1936.

Fig. 2.—*A*, perivascular reaction consisting predominantly of lymphocytes on the right side. The infiltration of the blood vessel on the left is mild. *B*, lymphocytic reaction in the meninges, with no appreciable degeneration of the cerebral cortex. Hematoxylin and eosin stain.
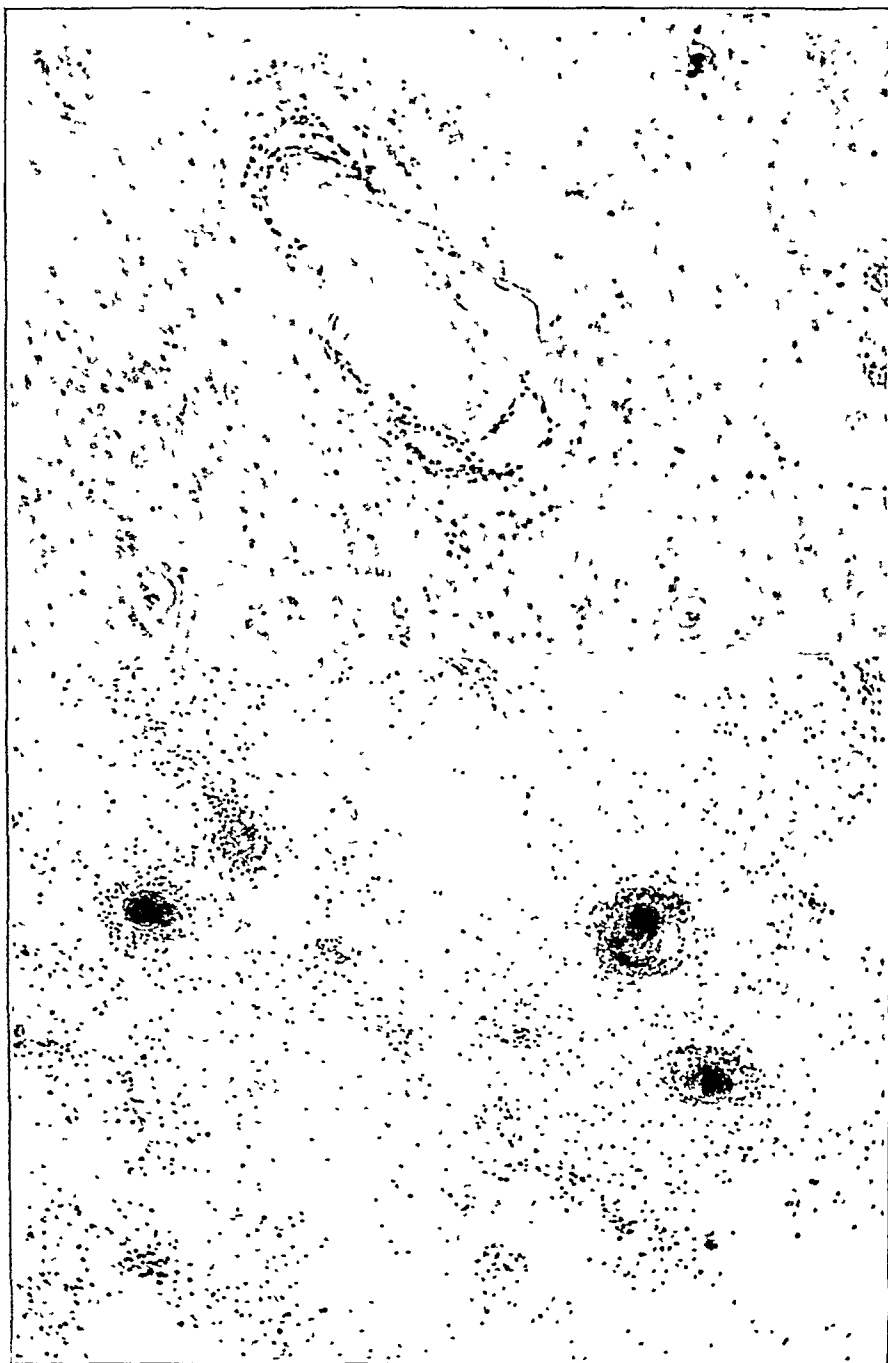
Fig. 5.—Perivascular edema and free edema in the parenchyma.

disease. Capillary hemorrhages have also been described (Siemerling and Raecke[77]). More often, congestion of blood vessels is present either in the parenchyma or in the meninges (fig. 4). Thickening of the meninges is not uncommon. Edema is also noted, especially in the acute stage, either in the parenchyma or in the perivascular spaces (fig. 5).

In diffuse sclerosis there is the same fundamental histologic picture. Even in cases in which the have been called polyblasts (Schröder[78] and Henneberg[79]), large mononuclear cells of the tissues, or histiocytes (Eisner[80]), macrophages (Hermel[81]) and epithelioid elements rich in protoplasm (Creutzfeld[82]). Thickening of the blood vessel walls and new formation of capillaries (Kogerer,[83] Bielschowsky and Henneberg,[11] Marie and Foix[4]) have also been noted. An increase in mesenchyme has also been reported (Neubürger,[13] Klarfeld,[84] Weimann,[16]
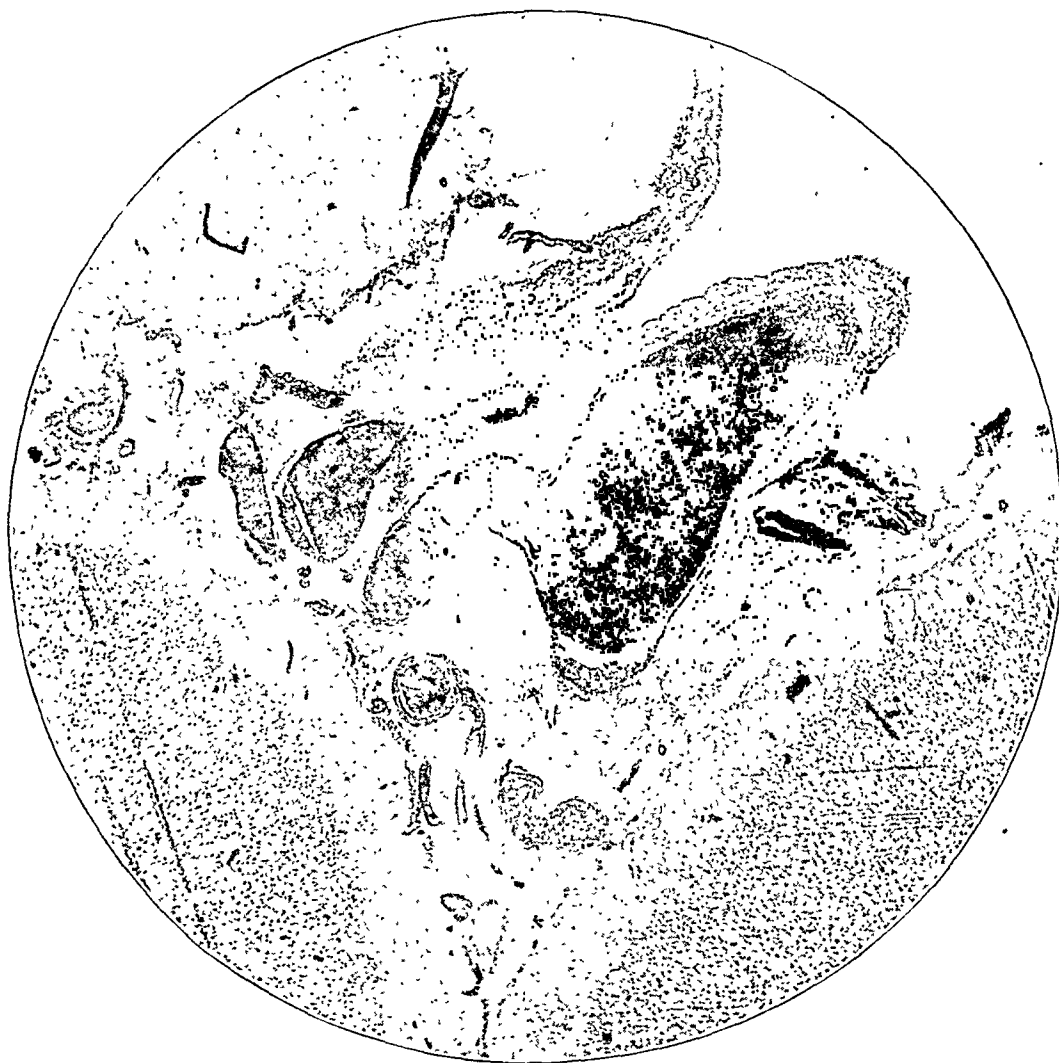
Fig. 4.—Marked congestion of the meningeal blood vessels. Hematoxylin and eosin stain.

process has been considered degenerative a small amount of perivascular infiltration has often been reported. In cases in which the disease is openly considered inflammatory the perivascular reaction, which is generally intense, is similar to that of multiple sclerosis. In some instances there is a cuffing of lymphocytes, and in others, a cuffing of compound granular corpuscles, often with a mixture of the two types which are distributed as in multiple sclerosis. Among the lymphocytes, the presence of large hematogenous mononuclear cells has also been reported; they

77. Siemerling, E., and Raecke, J.: Zur pathologische Anatomie und Pathogenese der multiplen Sklerose, Arch. f. Psychiat. 53:385, 1914.

78. Schröder, P.: Encephalitis und Myelitis: Zur Histologie der Kleinzelligen Infiltration im Nervensystem, Monatschr. f. Psychiat. u. Neurol. 94:87, 1918.

79. Henneberg, cited by Bouman.[8]

80. Eisner, W.: Ueber einen Fall von herdformig disseminierter Sklerose des Gehirns bei einem Saugling, Virchows Arch. f. path. Anat. 248:153, 1924.

81. Hermel, H., cited by Bouman.[8]

82. Creutzfeld, H. G.: Ueber eine eigenartige herdformige Erkrankung des Zentralnervensystems, Ztschr. f. d. ges. Neurol. u. Psychiat. 57:1, 1920.

83. Kogerer, H.: Beitrag zur Kenntnis der Encephalitis-periaxialis diffusa, Jahrb. f. Psychiat. 95:109, 1927.

84. Klarfeld, B.: Zur Frage der subakut verlaufenden diffusen Erkrankungen des Hemisphärenmarkes, Allg. Ztschr. f. Psychiat. 129:294, 1923.
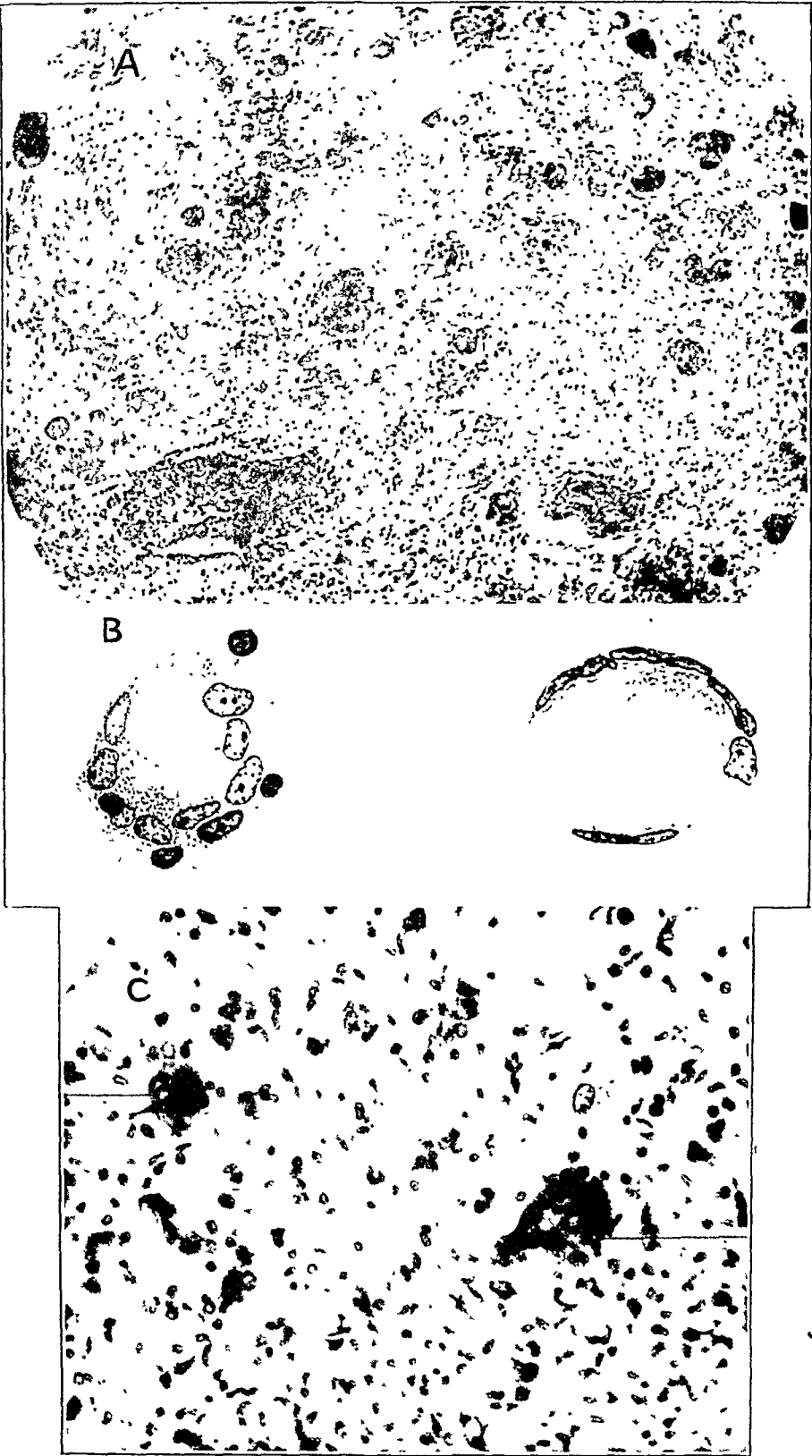
Fig. 6.—*A,* and *B,* giant cells in the parenchyma of the brain and details of giant cells in a case of multiple sclerosis (from Neubürger [96]) ; *C,* giant cells in the parenchyma of the brain in a case of demyelinating disease (from Hallervorden [98]).

Bouman[3] and Bielschowsky and Maas[85]). Hemorrhages were observed by Gagel[86]; Grainger-Stewart, Greenfield and Blandy[87]; Schaltenbrand[88]; Schröder[78]; Bouman[3]; Flatau,[89] and Kraus and Weil.[5] Necrotic areas and cystic degeneration were reported by Schilder,[90] Barré and associates,[91] Bodechtel and Guttmann,[92] Bouman,[3] Bielschowsky and Henneberg,[11] Wohlwill,[93] Marburg[94] and Gerstmann and Straussler.[95],

Of the pathologic changes of both multiple and diffuse sclerosis, one detail of the process which, in the light of the present investigation, seems important has been underemphasized, namely, the presence of giant cells in the areas of demyelination. These cells have been described by various authors. Neubürger[96] observed them free in the tissue or surrounding the blood vessels in a case of infantile multiple sclerosis (fig. 6 A and B) and concluded that they were of mesodermic origin; he illustrated their derivation from adventitial cells. These cells do not contain lipid material.

Creutzfeld,[97] in a case of acute multiple sclerosis of fifteen months' duration in a 15 year old girl, described multinucleated giant cells which he asserted to be of glial origin. Hallervorden,[98] in a case of a demyelinating disease of only five or six weeks' duration in a man aged 24, reported the presence of giant cells, which they also claimed to be of glial origin. Peters,[99] in 2 cases of encephalomyelitis, of approximately six weeks' and six months' duration respectively, which he found difficult to differentiate from multiple sclerosis, described giant cells in which he detected karyorrhexis. He predicated their origin from glia cells, though he never actually saw transitional stages between the macrogliocytes and the giant cells.

Hallervorden,[98] in a case of a disease which he concluded to be nonsuppurative disseminated encephalomyelitis, described the presence of giant cells of glial origin (fig. 6 C). Eisner,[80] in a case of disseminated sclerosis in an infant aged 4½ months, described the presence of giant cells not only in the brain but in the lungs and stated that their origin was probably from mesodermic elements presumably blood vessel walls.

Collier and Greenfield,[100] in a case of a child aged 5 years with diffuse sclerosis of fifteen months' duration, described in areas of "diffuse demyelination" the presence of large globoid cells with multiple nuclei under the capsule of the cell, arranged as a chain of thin, flattened structures. The authors concluded that these cells were of glial origin, foreign to most other forms associated with destruction of myelin, and stated the belief that they formed a prominent, and possibly an essential, feature of diffuse sclerosis.

Scherer[101] stated his opinion that a case of patchy sclerosis of seven months' duration, in which associated with typical patchy demyelination there were what he called neoplastic features, might represent a transition between multiple sclerosis and glioblastoma. Here, also, were numerous giant cells (figs. 7 A and B), which the author related to the glioblastic features of the process.

De Lange,[102] in a case of so-called Krabbe disease (diffuse infantile familial cerebral

85. Bielschowsky, M., and Maas, O.: Ueber diffuse und multiple Sklerose, J. f. Psychol. u. Neurol. 44:138, 1932.

86. Gagel, O.: Zur Frage der diffusen Hirnsklerose, Ztschr. f. d. ges. Neurol. u. Psychiat. 99:418, 1927.

87. Grainger-Stewart, T.; Greenfield, J. G., and Blandy, M. A.: Encephalitis Periaxialis Diffusa: Report of Three Cases with Pathological Examinations, Brain 50:1, 1927.

88. Schaltenbrand, G.: Encephalitis Periaxialis Diffusa (Schilder), Arch. Neurol. & Psychiat. 18:944 (Dec.) 1927.

89. Flatau, E.: Encephalopathia scleroticans progressiva, Encéphale 20:475, 1925.

90. Schilder, P.: Die Encephalitis periaxialis diffusa, Arch. f. Psychiat. 121:327, 1924.

91. Barré, Morin, Draganesco and Reys: Encéphalite periaxiale diffusa (type Schilder), Rev. neurol. 2:541, 1926.

92. Bodechtel, G., and Guttmann, E.: Zur Pathologie und Klinik diffusen Markerkrankungen, Ztschr. f. d. ges. Neurol. u. Psychiat. 138:544, 1932.

93. Wohlwill, F.: Ueber Encephalomyelitis bei Masern, Ztschr. f. d. ges. Neurol. u. Psychiat. 112:20, 1928.

94. Marburg, O.: Multiple Sklerose, in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1936, vol. 13, p. 546.

95. Gerstmann, J., and Straussler, E.: Zur Problemgebiet der Encephalomyelitis und der multiplen Sklerose, Arch. f. Psychiat. 93:182, 1931.

96. Neubürger, K.: Zur Histopathologie der multiplen Sklerose im Kindesalter, Ztschr. f. d. ges. Neurol. u. Psychiat. 76:384, 1922.

97. Creutzfeld, H. G.: Zur Frage der sogenannten akuten multiplen Sklerose, Arch. f. Psychiat. 68:484, 1923.

98. Hallervorden, J.: Eigenartige und nicht rubrizierbare Prozesse, in Bumke, O.: Handbuch der Geisteskrankheiten, Berlin, Julius Springer, 1930, p. 1063.

99. Peters, G.: Zur Frage der Beziehungen zwischen der disseminierten nichteitrigen Encephalomyelitis und der multiple Sklerose, Ztschr. f. d. ges. Neurol. u. Psychiat. 153:356, 1935.

100. Collier, J., and Greenfield, J. G.: The Encephalitis Periaxialis of Schilder: A Clinical and Pathological Study, Brain 47:489, 1924.

101. Scherer, H. J.: La "Glioblastomatose en plaques," J. belge de neurol. et de psychiat. 38:1, 1938.

102. de Lange, C.: Ueber die familiäre infantile Form der diffusen Gehirnsklerose (Krabbe), Ann. pædiat. 154:140, 1940.

sclerosis), described in association with the diffuse demyelination the presence of numerous cells, some of which were multinucleated, which she designated as epithelioid cells. She termed collections of such cells pseudotumors (fig. 7 C and D).

Figure 8 A illustrates the presence of multinucleated cells at the periphery of a patch of demyelination in a case of diffuse sclerosis in my own collection. In 1944 I had the opportunity to study a case of encephalitis which developed in the course of scarlet fever. In addition to a diffuse inflammatory reaction, which I ascribed to the "hyperergic" inflammatory process, there was a definite granulomatous formation, with typical giant cells in a limited area involving both the meninges and the underlying parenchyma of the brain (fig. 8 B).

The recent contribution of Putnam [103] on multiple sclerosis and encephalomyelitis makes clear the close pathologic analogy between these two conditions. A number of authors, among whom are Marburg,[34] Juba,[104] Pette,[105] Putnam [103] and myself, have stated the belief that the pathologic process of multiple sclerosis, characterized by glial scars interspersed with acute lesions, is only a chronic, relapsing form of the acute demyelinating disease. These conditions, in the words of Putnam, and in agreement with my own classification of the primary demyelinating diseases,

. . . include the type known as post-infectious and disseminated encephalomyelitis, Schilder's diseases, diffuse sclerosis, neuromyelitis optica. The histopathology of these disorders is fundamentally uniform, the differences being in location and intensity of the lesions.

The age of the patient, his individual resistance and the possible immaturity of the nervous system may also play a role in the diffusion of the pathologic process.

Other authors, however, among whom are Beck,[21] Hassin [106] and Lowenberg and associates [107]. concluded that ophthalmoneuromyelitis is an encephalomyelitis which differs from multiple sclerosis. Finally, another group of investigators, although not accepting the identity of multiple sclerosis and encephalomyelitis, stated that the two conditions are similar (Anton and Wohlwill,[17] Creutzfeld [82]).

Neubürger,[108] Gerstmann and Straussler [95] and Marcus [109] considered, in addition, the possibility of a mixed process, in which multiple sclerosis or encephalomyelitis might be associated with other inflammatory diseases of the central nervous system.

The encephalomyelitides present the same fundamental pathologic features as those described for multiple and diffuse sclerosis: areas of demyelination and often vascular and perivascular infiltration of hematogenous elements. These cells are mostly lymphocytes, though plasma cells and large mononuclear cells have been noted. Polymorphonuclear leukocytes constitute at times part of the exudate (Pette [110]). The inflammatory cells may be present for only a short time (Pette,[110] Walthard [111]). Perivascular hemorrhages were reported by Putnam [103] in cases of postvaccinal encephalomyelitis, and by Zimmerman and Yannet [112] in cases of encephalomyelitis accompanying chickenpox; hemorrhages in the meninges were described by Davison and Friedfeld [113] in cases of encephalomyelitis following rubella. Figure 9 illustrates the occurrence of hemorrhage in the parenchyma of the central nervous system in a case occurring in my experience.

With the acute demyelinating diseases, especially those following the infectious diseases of childhood, as with multiple and diffuse sclerosis, a pronounced microglial reaction surrounds the blood vessels and is often associated with a cuffing of lymphocytes. This histiocytic reaction, as a matter of fact, constitutes an outstanding pathologic feature (fig. 10). Thrombi of small venules have been described especially by Putnam and Alexander,[59b] and Kreider also encountered them in my cases of encephalitis com-

103. Putnam, T. J.: Multiple Sclerosis and "Encephalomyelitis," Bull. New York Acad. Med. 19:301, 1943.

104. Juba, A.: Die Beziehung zwischen multipler Sklerose und Encephalomyelitis .disseminata, Deutsche Ztschr. f. Nervenh. 143:268, 1937.

105. Pette, H.: Ueber die Pathogenese der multiplen Sklerose, Deutsche Ztschr. f. Nervenh. 105:76, 1928.

106. Hassin, G. B.: Neuroptic Myelitis Versus Multiple Sclerosis, Arch. Neurol. & Psychiat. 37:1083 (May) 1937.

107. Lowenberg, K.; DeJong, R. N., and Foster, D. B.: Neuromyelitis Optica, Tr. Am. Neurol. A. 67:59, 1941.

108. Neubürger, K.: Encephalitis epidemica bei multipler Sklerose, Zentralbl. f. d. ges. Neurol. u. Psychiat. 33:515, 1923.

109. Marcus, H.: Encephalitis lethargica, Sclérose en plaques: Eine differential diagnostische Studie, Acta psychiat. et neurol. 5:129, 1930.

110. Pette, H.: Postvaccinole Encephalitis, in Bunke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1936, vol. 13, p. 259.

111. Walthard, K.: Spatstadium einer Enzephalitis nach Masern, Ztschr. f. d. ges. Neurol. u. Psychiat. 134:176, 1930.

112. Zimmerman, H. M., and Yannet, H.: Non-suppurative Encephalomyelitis Accompanying Chickenpox, Arch. Neurol. & Psychiat. 26:322 (Aug.) 1931.

113. Davison, C., and Friedfeld, L.: Acute Encephalomyelitis Following German Measles, Am. J. Dis. Child. 55:496 (March) 1938.
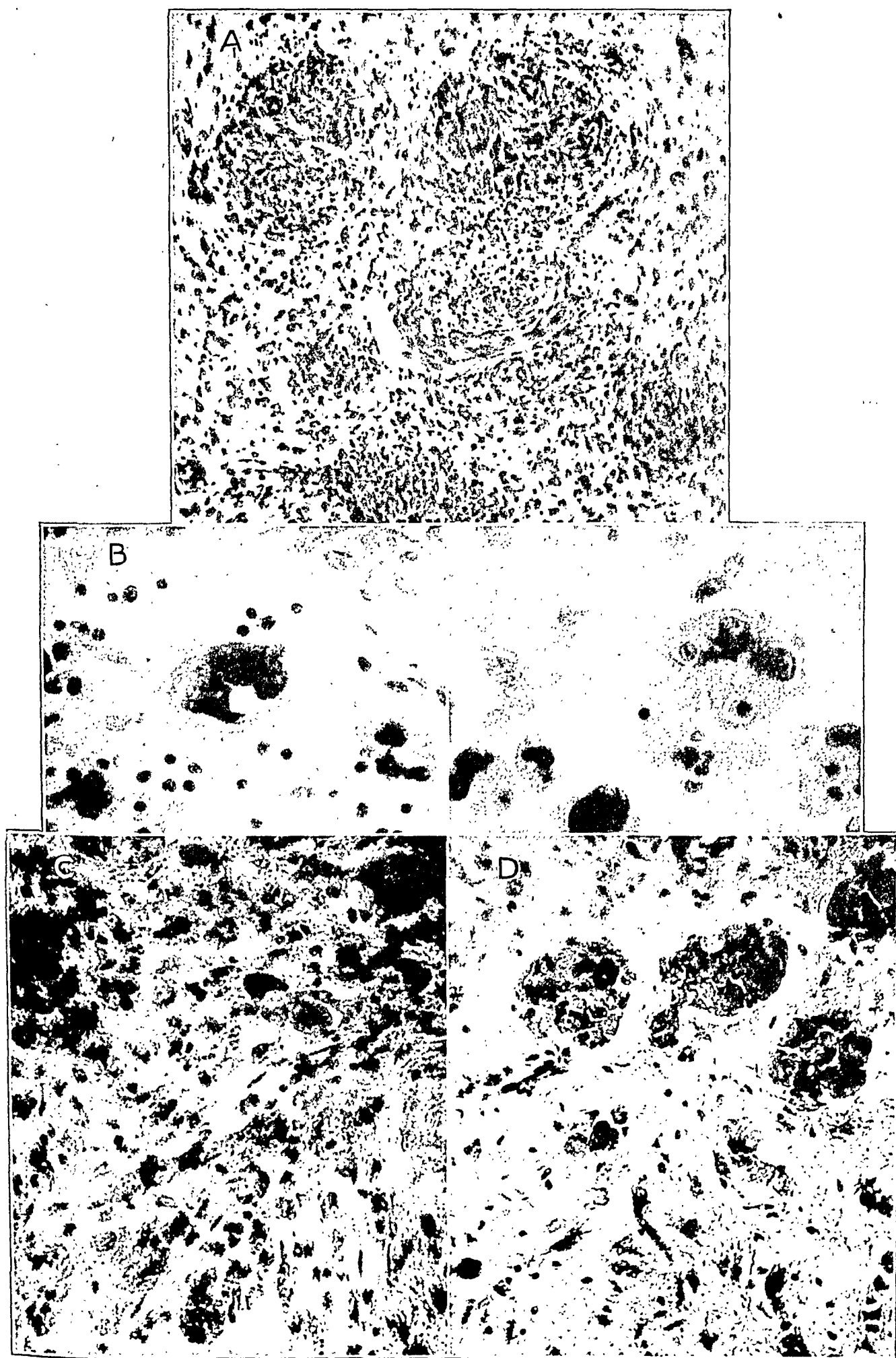
Fig. 7.—*A* and *B*, tumor nodules and details of cells in a case of multiple sclerosis (from Scherer [101]) ; *C* and *D*, giant epithelioid cells and pseudotumor formation in a case of Krabbe's disease (diffuse infantile familial cerebral sclerosis (from de Lange [102]).

plicating measles. Edema, degeneration of the vascular walls and necrosis are also present.

HISTOLOGIC FEATURES OF THE EXPERIMENTAL ALLERGIC REACTION

In 1903 Arthus[114] and Arthus and Breton[115] first described the pathologic features of cutaneous lesions associated with experimental anaphylaxis following repeated injections of horse serum. They described the occurrence of hemorrhages, edema and perivascular infiltration with polymorphonuclear cells, a condition which has since been known as the "Arthus phenomenon" (Nicolle).

Rössle,[116] in 1914, elaborating on the pathologic character of such a phenomenon, spoke of the "hyperergic" inflammatory reaction, in contrast to the normergic reaction of nonsensitized skin. Gerlach,[117] in 1923, made an extensive report on the histopathologic features of this condition in rabbits, rats and guinea pigs and followed the various phases of the pathologic reaction in groups of animals in which he had produced sensitization and shock with various doses of antigen and in the course of various periods.

114. Arthus, M.: Injections répétées de sérum de cheval chez le lapin, Compt. rend. Soc. de biol. 55:817, 1903.

115. Arthus, M., and Breton: Lesions cutanées produites par les injections de serum de cheval chez le lapin, Compt. rend. Soc. de biol. 55:1479, 1903.

116. Rössle, R.: Ueber die Merkmale der Entzundung im allergischen Organismus, Verhandl. d. deutsch path. Gesellsch. 17:281, 1914.

117. Gerlach, W.: Studien uber hyperergische Entzundung, Virchows Arch. f. path. Anat 247:294, 1923.

Gerlach confirmed the fundamental statements of Arthus, Breton and Rössle with regard to the appearance of edema, vasodilation, hemorrhages and perivascular infiltration of leukocytes. Hemorrhages were more pronounced in the subcutis.

It is important to note that in the course of the first twenty-four hours no lymphocytes were seen
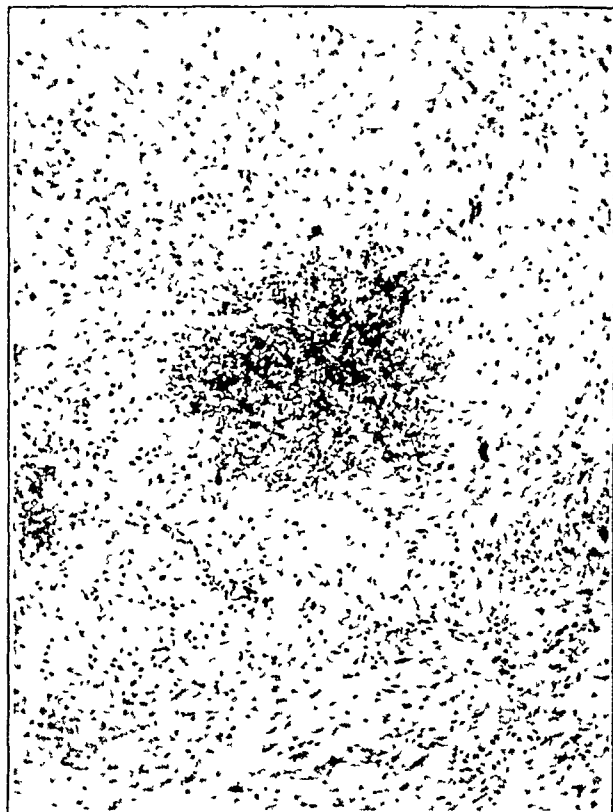
Fig. 9.—Hemorrhage in the nerve parenchyma in a case of acute disseminated encephalomyelitis Hematoxylin and eosin stain
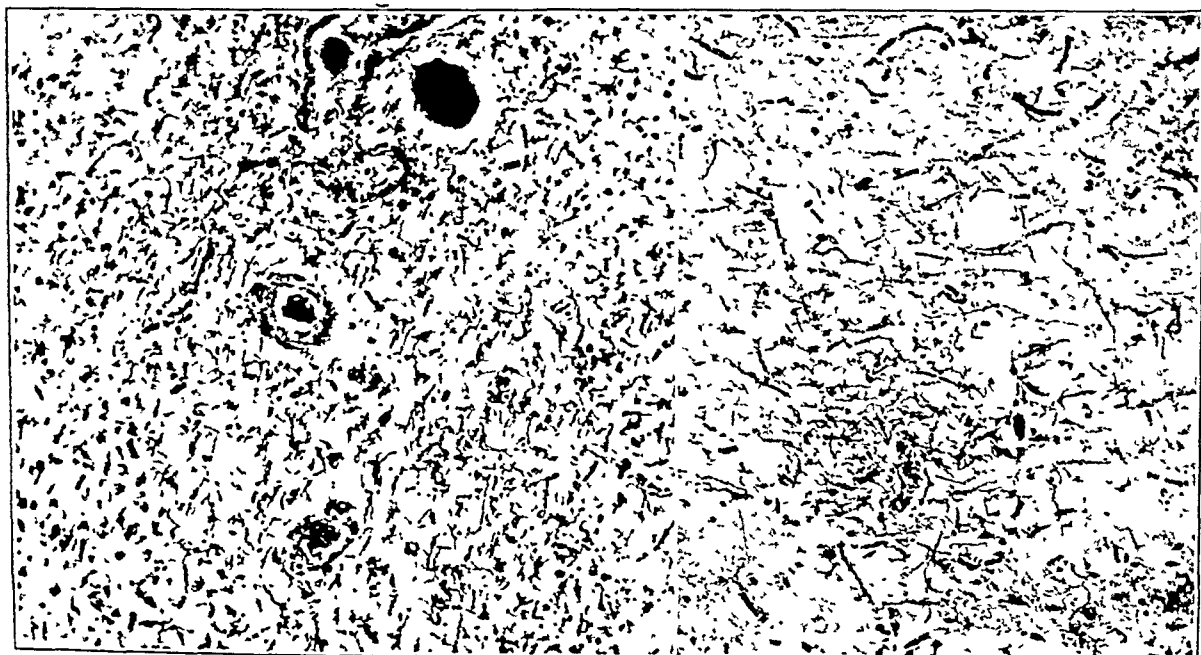
Fig. 10.—Pronounced perivascular histiocytic reaction in a case of measles encephalitis; Globus-Penfield modification of Hortega's method for microglia.

Fig. 8.—*A*, multinucleated cells at the periphery of an area of demyelination in a case of multiple sclerosis; hematoxylin and eosin stain. *B*, giant cells at the periphery of a granulomatous formation in a case of scarlet fever encephalitis (from Ferraro [75]) ; Van Gieson stain for connective tissue.

nerve tissue proper. In guinea pigs, rabbits and dogs which died after anaphylactic shock Stief and Tokay[128] observed two types of diffuse lesions, vascular and parenchymatous. The former were essentially hemorrhagic and the latter degenerative. Garcin, Bertrand, Laplane and Frumusan[129] obtained no significant changes in the nervous system by repeated intravenous injections of horse serum. However, after repeated weekly injections of human serum in rabbits, 2 of 5 animals showed changes characterized by neuronophagia, meningeal infiltrations and scattered microglial nodules. Similar lesions were produced in the brains of guinea pigs in which human serum was repeatedly injected by the intraperitoneal route. Baginski, Czarnecki and Hurynowicz[130] produced sensitization and shock in 6 rabbits with horse serum injected by the intravenous and subcutaneous routes. Examination of the brain showed enlargement of the Robin-Virchow spaces and proliferation of adventitial cells. In addition, scattered throughout the brain, cerebellum and medulla were small necrotic foci, 0.04 to 0.1 mm. in diameter, consisting of necrotic nerve cells, proliferating microglia cells and occasional leukocytes and lymphocytes.

Subsequently, Davidoff, Seegal and Seegal[69] in rabbits prepared with multiple sensitizing injections of horse serum and subjected to shock by one intracerebral injection observed an extensive inflammatory lesion in the brain, characterized by edema, serous exudate, hemorrhages and leukocytic infiltration. It is of interest to note that, though without emphasis, there was mention in this study of the change in the type of vascular reaction occurring in the later periods of the experiment. If animals were allowed to survive five or six days after the last injection, the central area of the lesion was considerably shrunken and sharply demarcated from the rest of the brain. Although polymorphonuclear cells were still present, the perivascular cells had by this time been replaced largely with lymphocytes.

Alexander and Campbell,[70] using a single intraperitoneal injection of horse serum, followed by a second injection of the antigen intra-

cerebrally, produced a lesion characterized by the presence of hemorrhages, vascular thrombosis, necrosis, demineralization, scavenger cells and a reaction of microglia cells, oligodendrocytes, and astrocytes.

Tokushige,[131] after sensitization of rabbits by means of intracerebral injections of foreign serum, reported that a second intracerebral injection resulted in a local cerebral Arthus phenomenon, with a rise in cerebrospinal fluid pressure and no change in blood pressure.

Miyahara[132] demonstrated that injection of the protein antigen into the blood stream of allergized animals brings on hemorrhagic infarcts in the brain, while introduction into the cisterna causes leptomeningitis and "inflammation" of the blood vessels.

In monkeys (Macacus rhesus), prepared by intravenous injections of antigen, followed by injections of the same antigen into the cerebral veins, Kopeloff, Davidoff and Kopeloff[72] succeeded in obtaining a severe Arthus-like reaction, accompanied sometimes by contralateral motor symptoms. Necropsy revealed in 1 animal an area of hemorrhagic discoloration and softening about the sylvian fissure on the left side of the brain. There was generalized edema of the left hemisphere, and the entire midline seemed to be shifted to the right. No histologic description accompanied this report. In 1941 Jervis and I, in collaboration with the Kopeloffs,[73] reported on the neuropathologic changes associated with experimental anaphylaxis in the monkey.

A review of the neuropathologic investigation which I have undertaken since has established the following new factors concerned with the vascular changes and the transformation of the perivascular reaction in relation to the chronicity of the experiments. While in cases of the acute stage the reaction was of hemorrhagic type, associated with an exudate of polymorphonuclear cells, in the cases in which the experiments involved more chronicity the hemorrhagic component was absent and the exudate was fundamentally one of lymphocytes to which histiocytes were added.

A summary of the observations follows.

MONKEY 15.—This animal, which received five intravenous injections of egg white, 10 cc. each at two day intervals, followed fifteen days later by one intravenous injection (10 cc.) of the same antigen and, finally, fifteen days later by an intracerebral injection of 0.2 cc. of the same antigen, died within fifteen hours after the intracerebral injection with severe symptoms of collapse. Histologic examination disclosed considerable engorgement of the blood vessels, especially of veins

128. Stief, A., and Tokay, L.: Durch experimentelle Serumanaphylaxie verursachte Veränderungen des Nervensystems, Ztschr. f. d. ges. Neurol. u. Psychiat. **150**:715, 1934.

129. Garcin, R.; Bertrand, I.; Laplane, R., and Frumusan, P.: Sur certaines lesions histologiques du nevraxe consecutives aux chocs anaphylactiques, Compt. rend. Soc. de biol. **118**:1190, 1935.

130. Baginski, S.; Czarnecki, E., and Hurynowicz, J.: Lesions histologiques due système nerveux des lapins en etat anaphylactique, Compt. rend. Soc. de biol. **130**:567, 1939.

131. Tokushige, J., cited by Urbach and Gottlieb.[138]

132. Miyahara, K., cited by Urbach and Gottlieb.[138]

in the perivascular infiltration or free in the tissues, though the walls of blood vessels were already seen to be undergoing necrotic changes. Soon after the end of twenty-four hours thrombus formation could be seen, with fibrin-forming exudate pouring from the necrotic walls of blood vessels. Thirty-four hours later lymphocytes and large mononuclear cells were present in the exudate, where multinucleated elements had already made their appearance. Forty-one hours later loose adventitial cells and fibroblasts were noted. Four days later numerous mobile cells, arising partly from connective tissue and partly from the adventitia, were noticed, and eight days later the cicatricial process of repair was prominent, with considerable neoformation of fibroblasts.

Gerlach stated that vascular spasm may occur, that the hemorrhages may be the result of stasis, that the presence of fibrin varies from one region to another, the amount being scant in the skin of the back and abundant in the skin of the ear, and that the pure "Arthus phenomenon" is expressed by hemorrhages and exudation of leukocytes, whereas the subsequent mobilization of histiocytes is presumably the result of local reaction to the antigen previously injected. A minimum dose of the antigen is necessary to produce the Arthus phenomenon, which Gerlach asserted to be the expression of a general reaction of wide significance.

In 1929 Klinge,[118] elaborating on the original statements by Weintrand and Stettner [119] that articular rheumatism and polioarthritis in children were the expression of an allergic reaction of the joints, began an extensive study of tissue anaphylaxis in these areas. His investigations have considerable importance because of the fundamental conclusion that in experimental local anaphylaxis a transformation of the histologic picture can be detected in relation to the dose of the antigen and to the time element. In the early stages of the anaphylactic reaction following large doses of antigen and repeated sensitization to the vascular reaction was a stormy leukocytic phenomenon associated with hemorrhage (Arthus phenomenon). With smaller amounts of antigen and more protracted sensitization a reaction was produced in which both leukocytes and mononuclear cells participated. After more protracted sensitization in the course of many months, the histologic reaction underwent a total change from a polymorphonuclear to a monocytic-

histiocytic type, without further participation of polymorphonuclear cells, but with an occasional tendency to granulomatous formation. Thus Klinge confirmed conclusions which Graff [120] had already substantially reached in 1927.

Klinge's work was followed by studies by other investigators, among whom were Vaubel,[121] Knepper,[122] Knepper and Waaler [123] and Epstein.[124] These authors were concerned especially with such factors as tissue and organ susceptibility to anaphylactic reaction and the importance of various precipitating factors in determining the hyperergic inflammatory reactions. Of these factors, trauma, hyperventilation, overexertion, heat and cold and the influence of various hormones and cytotoxins were studied.

In general, these authors confirmed the histopathologic observations of Klinge, particularly with respect to the occurrence of granulomatous formations in the stage of the lymphocytic-histiocytic reaction. Necrosis of blood vessel walls, proliferation of the intima, formation of hyaline thrombi and hyperplasia of the lymphoid apparatus were also reported.

During investigations on the anaphylactic reaction of various organs, Rachmanow [125] noted degenerative alterations in the neuron cells of animals which had died in anaphylactic shock. Weinberg,[126] in cases of severe shock, reported perivascular infiltration, hemorrhages, occasional thrombosis, diffuse degenerative changes of neuron cells and alterations of the myelin sheaths. Feuillié and Thiers [127] produced shock by injecting intravenously into a dog five doses of Witte's peptone (0.1 Gm. per kilogram of body weight) over a period of two weeks, after which they reported lymphocytic infiltration of the pia at the level of the lumbar region but no changes in the

120. Graff, S.: Rheumatismus infectiosus, Deutsche med. Wchnschr. 53:708, 1927.

121. Vaubel, E.: Die Eiweissüberempfindlichkeit (Gewebshyperergie) des Bindegewebes, Beitr. z. path. Anat. u. z. allg. Path. 89:374, 1932.

122. Knepper, R.: Ueber die Lokalisierung der experimentellen allergischen Hyperergie, Virchows Arch. f. path. Anat. 296:364, 1935.

123. Knepper, R., and Waaler, G.: Hyperergische Arteritis der Kranz- und Lungengefässe bei funktioneller Belastung, Virchows Arch. f. path. Anat. 294:587, 1935; Lungenbefunde beim akuten anaphylaktischen Shock des Kaninchens, ibid. 296:465, 1935.

124. Epstein, cited by Vaubel.[121]

125. Rachmanow, M.: Lésions nerveuses dans l'anaphylaxie séreuse et vermineuse, Compt. rend. Soc. de biol. 75:317, 1913.

126. Weinberg, E.: Histologische Veränderungen im Gehirn während des anaphylaktischen Shocks, Ztschr. f. d. ges. Neurol. u. Psychiat. 87:451, 1923.

127. Feuillié, E., and Thiers, J.: Production expérimentale de sclérose dans le système nerveux, Rev. neurol. 1:606, 1926.

118. Klinge, F.: Die Eiweissüberempfindlichkeit (Gewebsanaphylaxie) der Gelenke, Beitr. z. path. Anat. u. z. allg. Path. 83:185, 1929.

119. Weintrand and Stettner, cited by Klinge.[118]
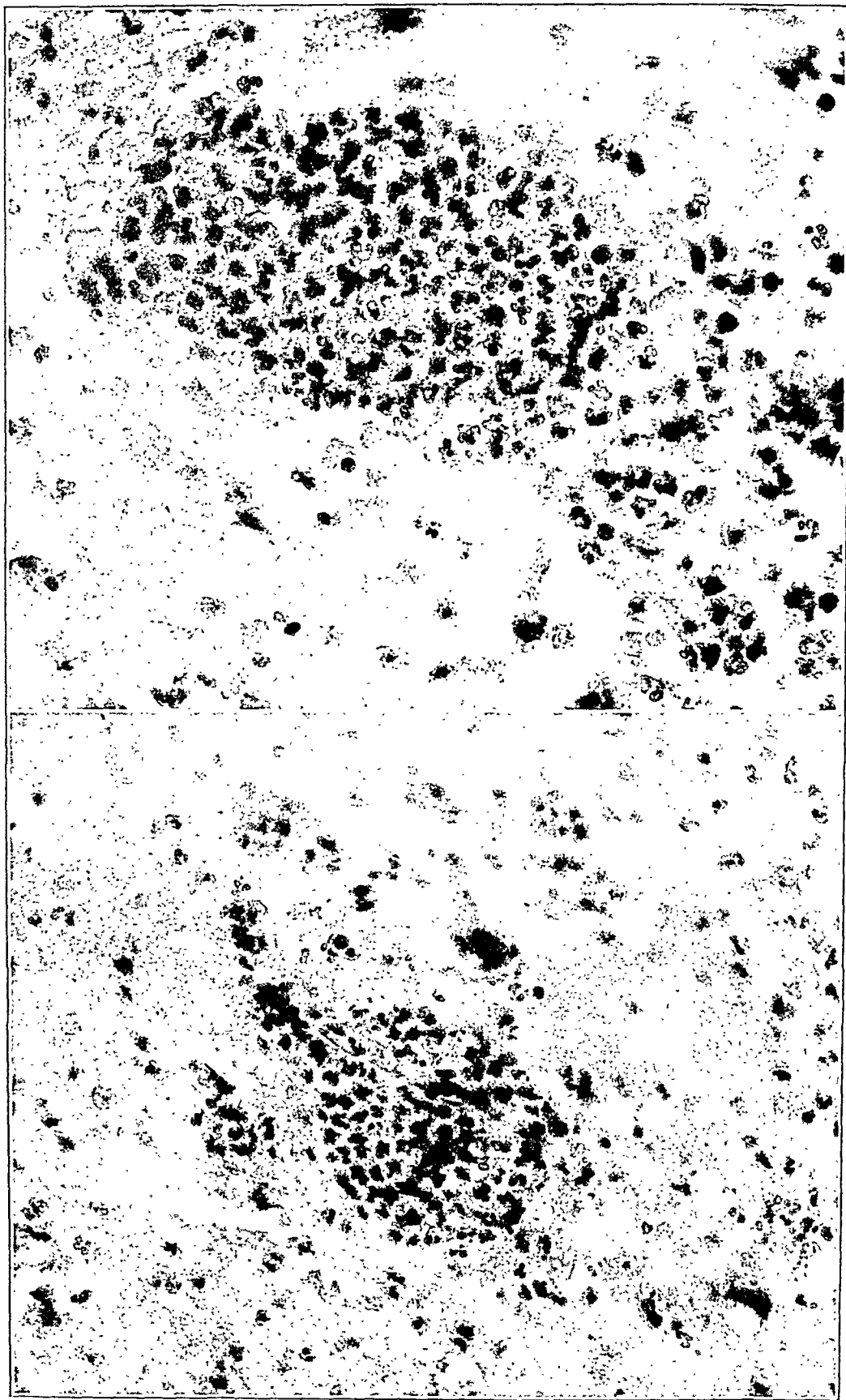
Fig. 13.—Perivascular exudate, formed almost exclusively of polymorphonuclear cells.   Hematoxylin and eosin stain.

Fig. 11.—*A* and *B*, pronounced vascular congestion and hemorrhages in the meninges of the rabbit. Hematoxylin and eosin stain.

Fig. 12. Numerous hemorrhagic petechiae of the brain and parenchyma. Hematoxylin and eosin stain.

Fig. 15.—Thrombosed blood vessels surrounded by a few polymorphonuclear cells. Hematoxylin and eosin stain.

in the meninges. The dilatation of veins could be followed in the septums. In addition to the vascular engorgement, free hemorrhages were noted in the arachnoid covering (fig. 11), as well as in the subpial area. The red blood cells in the dilated blood vessels or in the free hemorrhages were at times individually outlined and well preserved; at other times homogenization of the cells was dominant. In the subpial areas one could recognize individual blood vessels surrounded by large numbers of red blood cells. The red blood cells generally formed a homogeneous mass, though it was not unusual to note either individual red cells or large collections of these cells still possessing a normal appearance. In the midst of the hemorrhages one often recognized pigment, probably of hematic origin, either free or included in phagocytic elements. The hemor-
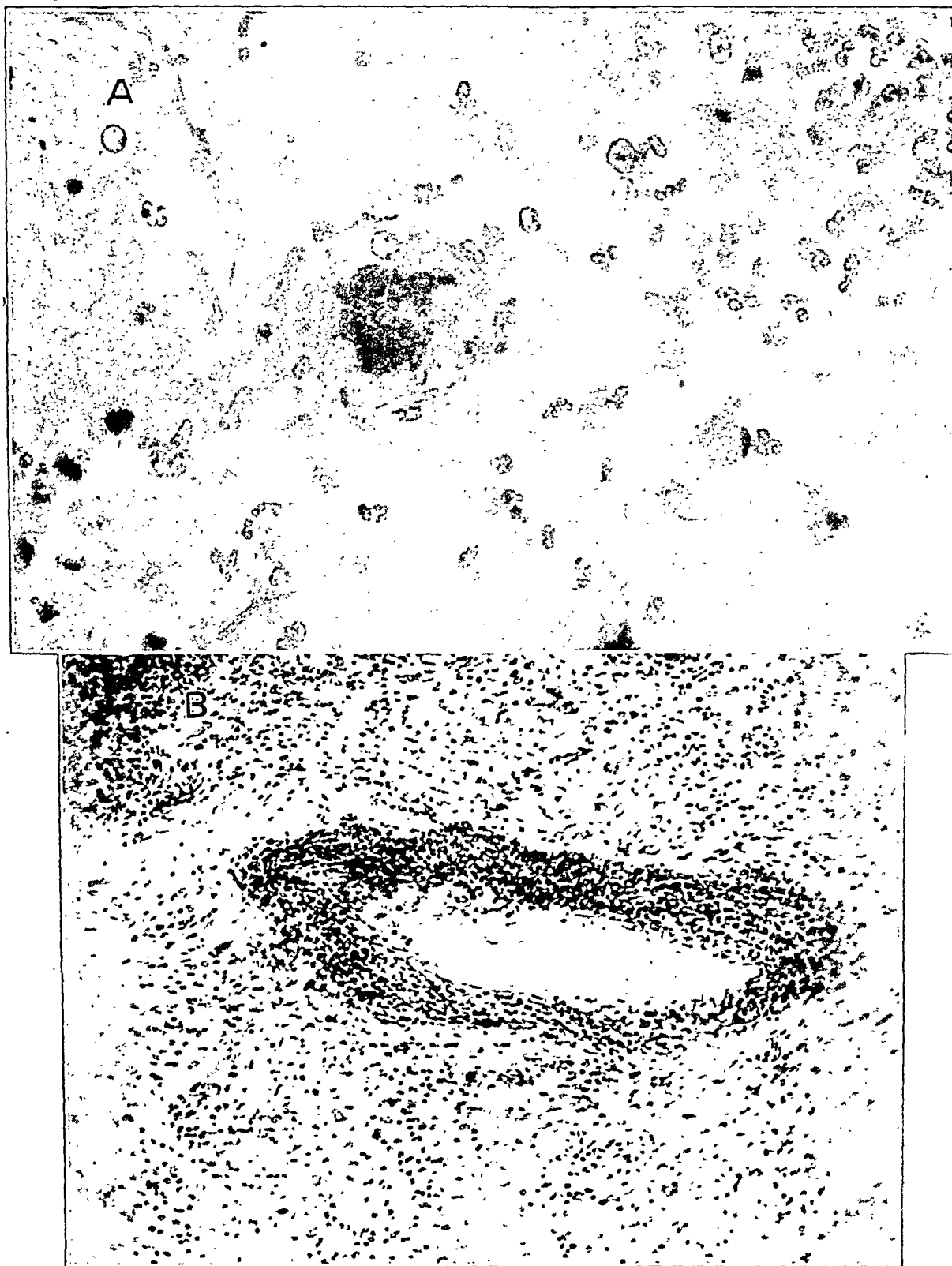
Fig. 14.—*A*, hyaline thrombus; hematoxylin and eosin stain. *B*, perivascular infiltration, formed predominantly lymphocytes; Nissl stain.

hemorrhages at places extended into the external layers of the cortex.

In the brain substance itself numerous petechial hemorrhages were noted, which in certain areas extended deep into the cortex, reaching the white matter (fig. 12). The petechial hemorrhages were chiefly about the blood vessels. Some of the petechiae were confluent, forming a large hemorrhagic mass, in which

rhages were not diffuse but appeared concentrated in areas in the immediate vicinity of the injected antigen. Farther away there were no hemorrhages, although engorgement of blood vessels was a feature of wider distribution.

Next to hemorrhages, edema was conspicuous in the same areas of distribution. It was present either free in the tissue or more localized in the perivascular

spaces of His. At times it was more circumscribed in the Virchow-Robin spaces. The fluid had a homogeneous appearance and generally did not stain, though occasionally it was slightly blue. In the vicinity of the hemorrhages, the edema invaded the nerve parenchyma itself, and the perineuronal spaces were dilated. Acute swelling of oligodendrocytes contributed to the edematous appearance of the tissue.

In addition to hemorrhages and edema, the perivascular reaction constituted an outstanding feature. At this stage the exudate was formed almost exclusively of polymorphonuclear cells (fig. 13). The majority of the cells were neutrophils, and only occasionally were mast cells or eosinophils present. The leukocytes, collected around the blood vessels, were occasionally seen apparently free in the surrounding tissue.

Study of the blood vessel walls also revealed interesting facts. In some of the blood vessels subendothelial edema was evident. Other vessels disclosed homogenization of the walls, especially of the media, an expression of early degenerative change. No appreciable thickening of the adventitia was noted at that stage.

At this stage there was already, however, a tendency toward thrombus formation. This was expressed as an increase in the zone of plasma, which in certain cases occupied a good fourth or fifth of the lumen of the blood vessels, and as early pavementing of the leukocytes, the middle third of the stream being left free for the plasma zone and the central zone being occupied by red blood cells. Early thrombi, to which platelets and fibrin contributed, were seen here and there, and gradual hyalinization of the mass followed, with partial or complete occlusion of the lumen of the blood vessel (fig. 14 *A*). No appreciable organization of thrombi was detectable at this stage.

MONKEY 14.—This animal received five intramuscular injections of 0.2 cc. of antigen (egg white) at two day intervals, followed in fifteen days by one intravenous injection of 10 cc. of the same antigen and, finally, fifteen days later by an intracerebral injection of 0.2 cc. of the same antigen. Death occurred six days after the intracerebral injection. During these six days the monkey had convulsions and displayed paretic symptoms on the side opposite that of the intracerebral injection.

The vascular reaction in this animal had undergone a' striking change. The hemorrhagic features described in monkey 15 were present also in this animal; in addition, in the central, necrotic portion of the area of injection one could see that resorption of the red blood cells was taking place, as evidenced by homogeneous masses, in which none or few individual red cells were recognizable. The meninges did not disclose the pronounced congestion or the free hemorrhages noted in monkey 15 outside the site of injection. Perivascular hemorrhages were mild in extent and intensity as compared with' the hemorrhages in the preceding animal.

At the periphery of the necrotic area the change in the type of perivascular exudate was more evident. Instead of the intense reaction, and almost exclusive presence, of polymorphonuclear leukocytes, lymphocytes and large mononuclear cells seemed to form the bulk of the exudate (fig. 14 *B*). Here and there among the lymphocytes a few polymorphonuclear cells could be seen. The perivascular cuffing of lymphocytes was more frequent about blood vessels in which definite thrombi were not present. When thrombi were present, they were mostly of the hyaline type, with no outstanding organization. About some of the thrombosed blood vessels occasional polymorphonuclear cells were present (fig. 15).

Progressive changes in the blood vessel walls had made their appearance at this stage. Definite thickening of the adventitia, with notable proliferation of the intima, leading to partial occlusion of the lumen, was noticeable (fig. 16).

In addition to lymphocytes, the presence of large mononuclear cells constituted one of the important variations in the perivascular exudate occurring at this stage. These large cells, presumably originating from blood elements or from the adventitia (adventitial cells or polyblasts), were present in increasing numbers as the chronicity of the reaction increased. A tendency for these cells to fuse together, especially in the adventitia, was already detected.

A notable histiocytic reaction had also made its appearance, and compound granular corpuscles were seen surrounding the lymphocytes or intermingled in the perivascular exudate. The compound granular corpuscles loaded with fat substances stained characteristically with scarlet R.

These vascular changes were noted not only in the immediate vicinity of the area of injection of the antigen but in remote portions of the central nervous system, such as the midbrain, the pons, the medulla oblongata and the cerebellum, which had no direct contact with the injected antigen.

MONKEY 17.—This animal received eleven intracerebral injections of 0.2 cc. of antigen at weekly intervals, followed fifteen days later by eight additional intracerebral injections and, finally, fifteen days later, by an additional intracerebral injection. Thirty days later one intravenous injection of 10 cc. of antigen was administered, followed twenty-five days later by a final intravenous injection of the same antigen.

In this animal, for which the duration of the experiment lasted at least twenty-four weeks, the pathologic reaction had substantially changed. No hemorrhages were seen, and no polymorphonuclear leukocytes were noted in the perivascular exudate, where, instead, lymphocytes, large mononuclear cells and histiocytes predominated. At this stage the presence in the perivascular exudate of large polygonal cells of somewhat epithelioid appearance was outstanding. These cells, mixed with lymphocytes, showed a tendency to coalesce and form giant cells. The presence of these giant cells was also characteristic. They were noted in the perivascular exudate or, at times, within the walls of a blood vessel. They were present not only in the cerebral parenchyma but in the meninges (fig. 17).

Of importance at this stage was the presence of miliary granulomas in which typical giant cells were present. These granulomas were scattered in the various layers of the cortex, some being larger than others and histologically of various complex structures, the reaction being at times limited to the appearance of only one or two giant cells surrounding or occupying the lumen of the blood vessel (fig. 18).

Immediately surrounding the blood vessels, in addition to the large mononuclear, epithelioid-like and giant cells, were a large number of microglia cells, histiocytes of the central nervous system, which were undergoing proliferation and all stages of transformation, for the most part, into compound granular corpuscles.

Of interest was the fact that the reaction was not always of the same type, either in intensity or completeness. Sometimes the histiocytic reaction predominated; in other areas the granulomatous reaction, and in others the lymphocytic reaction was dominant, and the other components were less evident, or even absent. Thus,
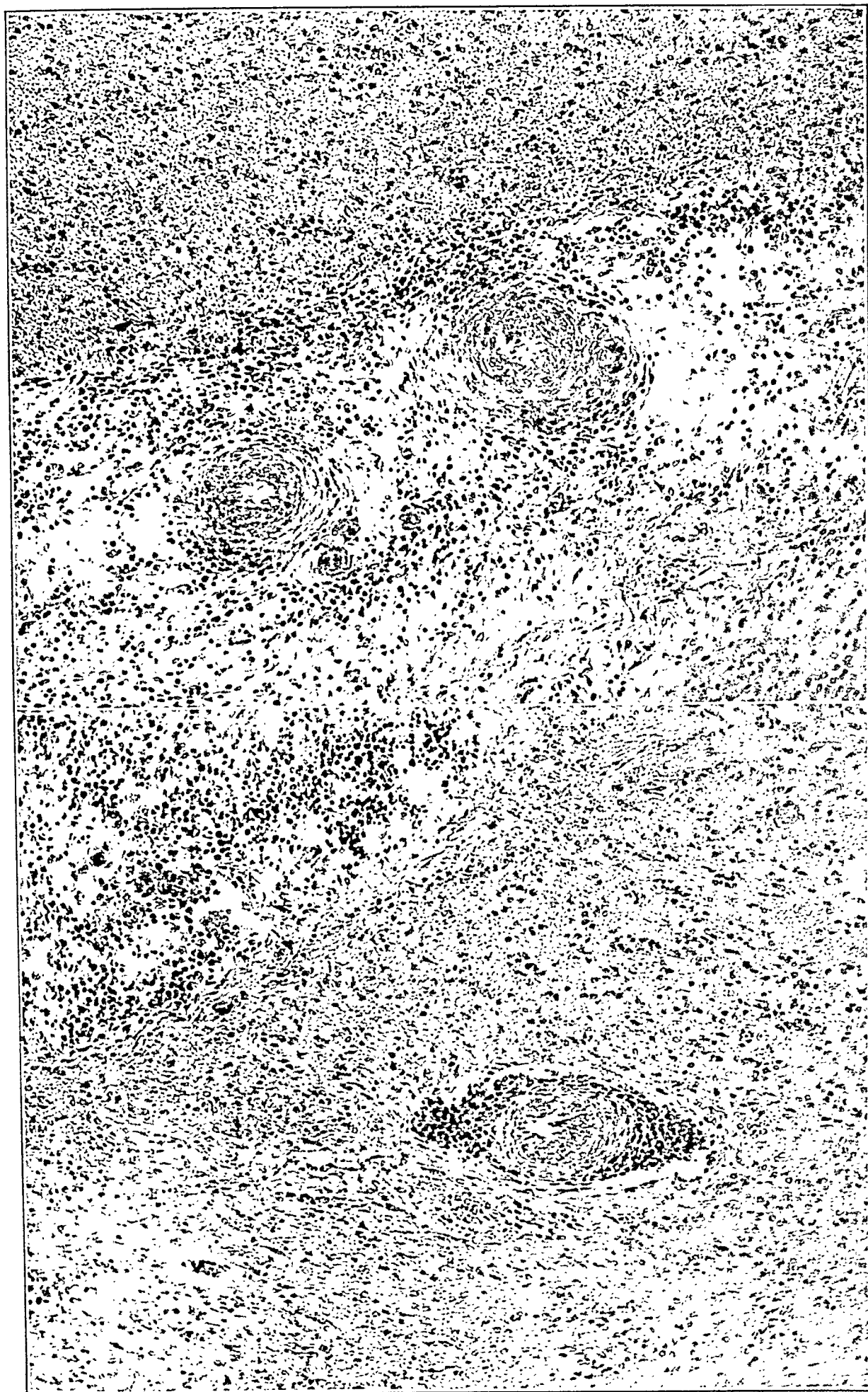
Fig. 16.—Progressive changes in the blood vessel walls, with marked proliferation of the intima. Hematoxylin and eosin stain.

The 7 monkeys reported on in ·our study received from a minimum of twenty-nine injections to a maximum of one hundred and three injections, and the duration of the observation varied from a minimum of one hundred and twelve days to a maximum of four hundred and five days.

The pathologic changes in the brain were fundamentally similar with respect to the type of

An outstanding feature of the process refers to the absence of any pathologic change referable to the acute "Arthus phenomenon." No hemorrhages were noted in the meninges or in the parenchyma of the brain, either in the form of perivascular petechiae or free in the tissues. Neither was the exudate formed predominantly of polymorphonuclear cells. We noted no stage of the perivascular reaction comparable to the
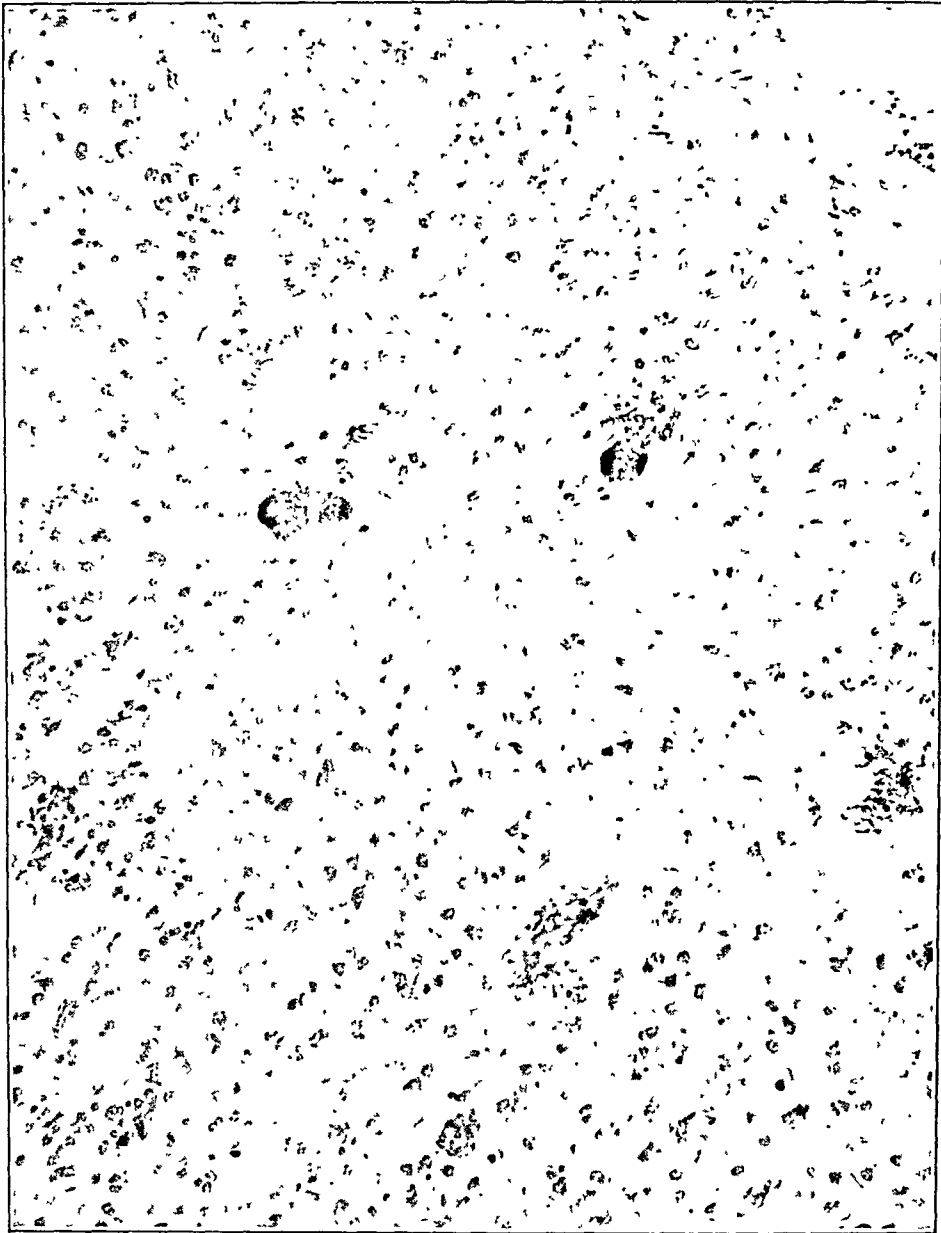
Fig. 18.—Giant cells surrounding blood vessels in the cerebral cortex. Hematoxylin and eosin stain.

tissue reaction. The severity of the reaction varied from one animal to another but was not related to the number of the injections. Monkey 673, which received thirty-three injections in the space of one hundred and twenty-six days, presented as typical a ·pathologic picture as did monkey 696, which received one hundred and three injections in the course of four hundred and five days.

early stages of the reaction following intracerebral injections of antigen.

The perivascular reaction was fundamentally one of lymphocytes and histiocytes and could be classified under three main types: In the first type the cellular reaction consisted mainly of compound granular corpuscles. In the second type, the infiltration consisted mainly of lymphocytes; here and there, in certain areas, poly-

in monkey 43, which received the antigen always by intracerebral injection except for the last injection, which was given intravenously, while the lymphocytic-histiocytic reaction was the dominant feature, no miliary granulomas were present, and only occasional giant cells were encountered.

Also, the presence of the pronounced histiocytic reaction, with formation of individual giant cells or small granulomas, was not limited to the areas of injections of the antigen but, as with the early stage of the reaction, was noted in distant regions, such as the medulla

The hypothesis that antibodies specific for a given organ are responsible for certain diseases of unknown etiology has been brought forward many times, but little evidence has been produced that organ-specific antigens actually occur. However, as far as the central nervous system is concerned, recent experiments (Witebsky and Steinfeld; Schwentker and Rivers) have demonstrated that emulsions of heterologous brain tissue when repeatedly injected into rabbits are capable of inciting antibodies specific for the rabbit brain. The

Fig. 17.—Large giant cell in the meninges. Hematoxylin and eosin stain.

and the cerebellum, where no direct contact of the antigen with the tissue had been established.

Prior to this investigation, Jervis and I,[68] following the lead of experiments by Rivers, Sprunt and Berry[66] and Rivers and Schwentker,[67] had reported in 1940 on the cerebral pathologic changes following the intramuscular injection in monkeys of fresh aqueous emulsions and an alcohol-ether extract of normal rabbit brain.

In discussing the mechanism of production of the cerebral lesions, we stated[68]:

antibodies can be demonstrated either by complement fixation tests or by precipitin reactions. Further, brain-specific antibodies are also produced by an alcohol extract of brain provided an antigenically active protein is added. The reacting antigen appears to be a lipoid functioning as a haptene, which is actuated by a protein. It will be noted that in the present experiments a lipoid substance was contained in both the emulsion and the ether-alcohol extract, and a protein was doubtless present in the emulsion. There is, therefore, enough justification for assuming that the lesions in the brain may be associated with the development of antibodies specific for brain.
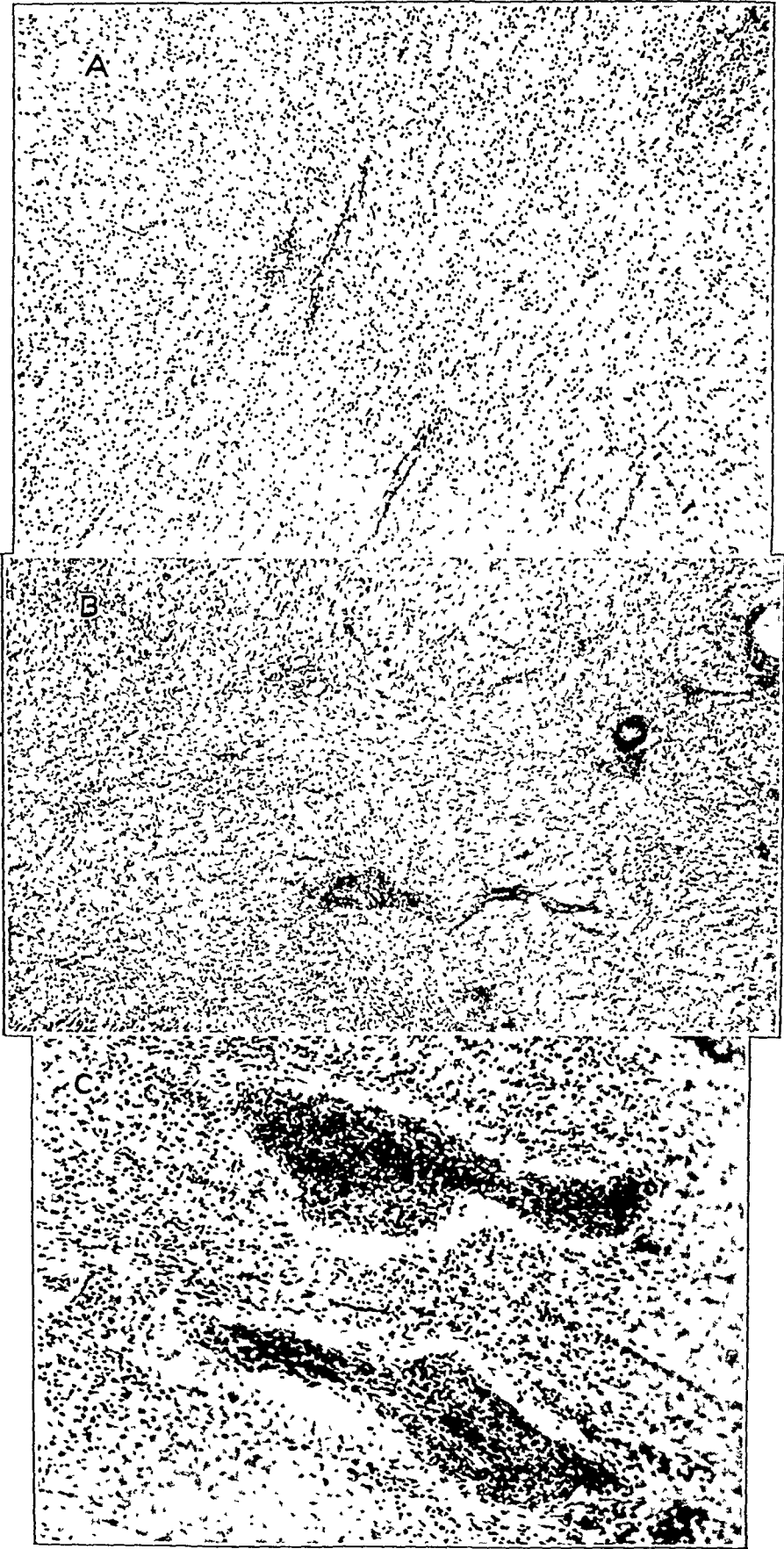
Fig. 20.—Three degrees of intensity of the perivascular reaction. *A*, very mild; *B*, moderate, and *C*, pronounced. Nissl stain.
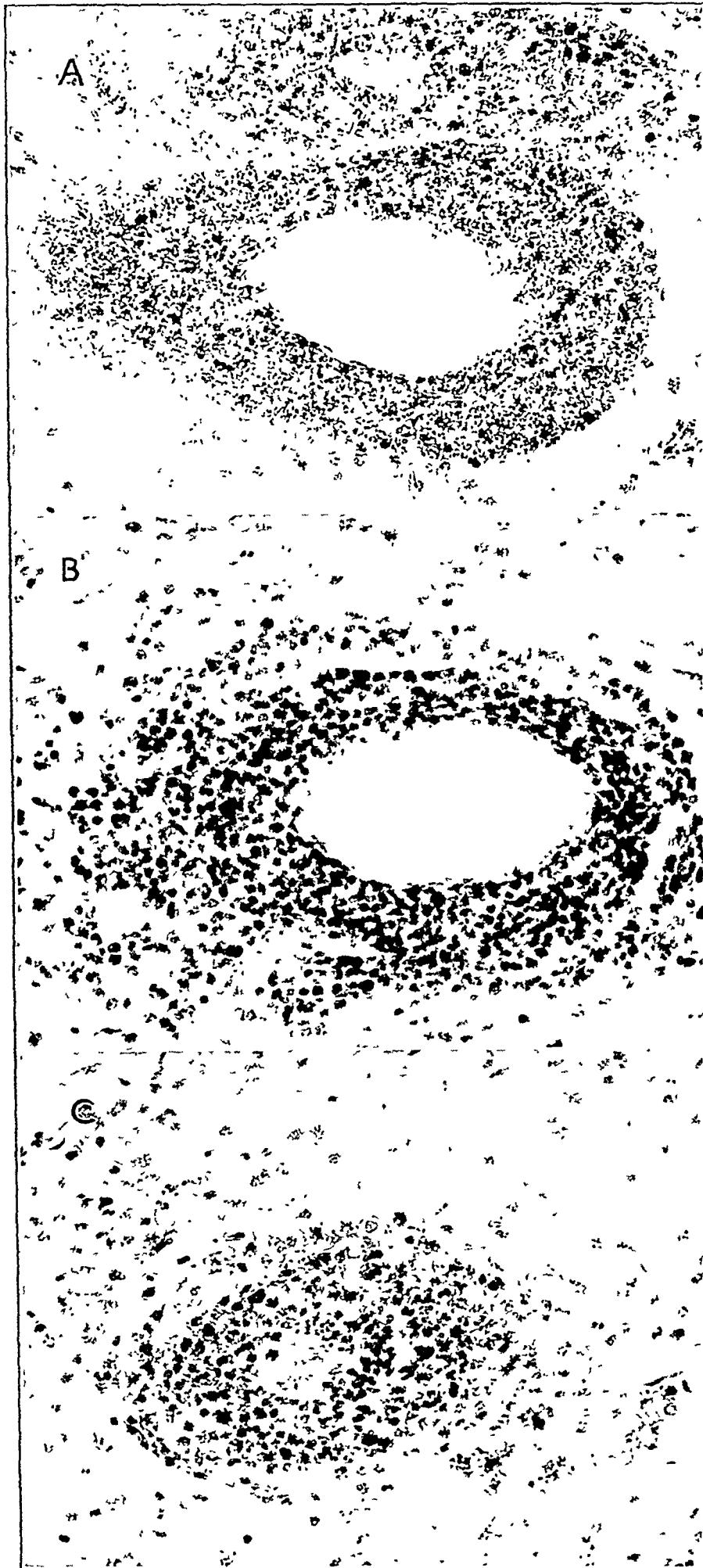
Fig. 19.—Various types of perivascular reactions. *A*, compound granular corpuscles; *B*, lymphocytes; *C*, mixture of the two types of cells. Nissl stain.

Figure 21 illustrates two stages of necrosis. In the necrotic area, in addition to fragments of nerve elements, compound granular corpuscles were noted in considerable numbers. The pathologic changes were widely distributed throughout the brain but were most frequent in the white matter of the hemisphere. The diencephalon and large mononuclear cells were present in the exudate and gave the impression of originating from the cellular elements of the adventitia. A large number of these cells were polynucleated and constituted characteristic giant cells of the foreign body type; these giant cells were numerous and in places were an outstanding feature of

Fig. 22.—Numerous giant cells in the midst of a perivascular reaction. Nissl stain

the mesencephalon were also distinctly involved. The major intensity of the pathologic process occurred, however, in the pons, the medulla oblongata and the cerebellum.

Not only lymphocytes or a combination of lymphocytes and compound granular corpuscles was noted about the blood vessels, but often the histologic process (fig. 22). In addition to their apparent origin from large mononuclear cells or from cells of the adventitia, their origin from the histiocytes of the region (microglia cells) could not be excluded. The impression was received that in some cases fusion of histiocytes resulted in giant elements.

morphonuclear and plasma cells were seen. In the third type, both hematogenous elements and histiocytes — compound granular corpuscles — were present, with the compound granular corpuscles generally distributed at the periphery and

tion and early organization were encountered. Finally, the development of some of the small blood vessels were occluded as a result of granulomatous formations in the blood vessel walls themselves especially in the intima.
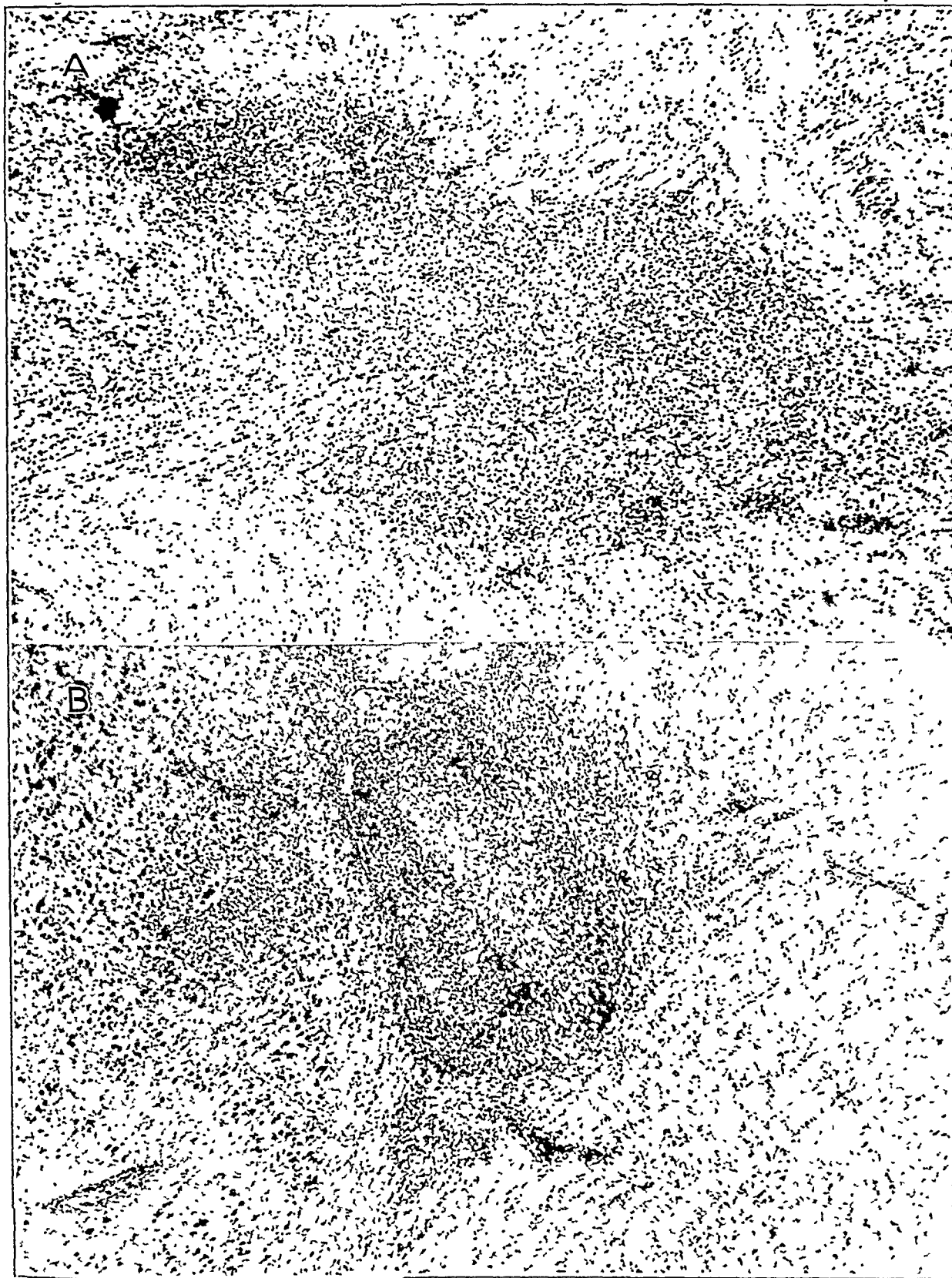
Fig. 21.—Early (*A*) and advanced (*B*) stages of necrosis. Nissl stain.

the lymphocytes occupying the central portion of the mass of exudate (fig. 19).

A second study of the slides revealed degeneration of blood vessel walls, especially hyalinization and thickening of the adventitia. Thrombi were at times represented by plugs of degenerated red blood cells. In some of the thrombi fibrin forma-

All gradations in the intensity of the perivascular reaction could be seen from very mild to intense. Figure 20 illustrates the occurrence of a mild, a moderate and a pronounced perivascular reaction. The intensity of the parenchymal damage also varied from one area to another.

Hemorrhages.—In cases of acute multiple sclerosis and acute disseminated encephalomyelitis hemorrhages of various distribution have been reported. Hemorrhages, both large and small, are an important feature of the acute stage, or Arthus phenomenon, of experimental general or cerebral anaphylaxis.

The paucity in general of hemorrhages in the chronic stages of disseminated or diffuse sclerosis has its parallel in the gradual disappearance of hemorrhages in the more advanced stages of experimental cerebral anaphylaxis.

Involvement of Blood Vessel Walls.—Degeneration (homogenization, hyalinization, arteriofibrosis and thickening) of the walls of blood vessels has been reported in cases of both acute and chronic disseminated sclerosis, diffuse sclerosis and acute disseminated encephalomyelitis. Degeneration and necrosis of the blood vessel walls is a common feature of acute experimental anaphylaxis.

Thrombus Formation.—In cases of acute disseminated sclerosis, diffuse sclerosis and acute encephalomyelitides Putnam[103] and his co-workers demonstrated the presence of thrombi, for which at times special staining methods are needed. These venous thrombi, according to Putnam, play an important role in the production of demyelination.

Thrombi are associated with experimental anaphylaxis of the skin, joints, heart and lungs, as well as of the brain. All stages of thrombus formation may be observed, accumulation of fibrin, pavementing with leukocytes and formation of red cell and hyaline thrombi to actual organization.

Distribution of Perivascular Reaction.—In acute encephalomyelitis the perivascular reaction is often predominantly perivenous. In multiple sclerosis, especially the acute type, the perivascular reaction is also predominant about the veins, though later it involves the capillaries and arteries.

In experimental cerebral anaphylaxis, as well as in anaphylaxis of other organs, investigators have emphasized the predominance of perivenous reaction.

Type and Intensity of Perivascular Infiltration.—In cases of acute and chronic disseminated sclerosis, acute and chronic diffuse sclerosis and acute encephalomyelitis perivascular infiltration, in various degrees, at times prominent, is almost always present. It is true that in some cases of chronic multiple sclerosis the perivascular reaction is minimal, but one must consider that the chronic type has run a course of many years and

that the original pathologic picture has presumably undergone extensive modifications. The cellular elements which compose the exudate in these demyelinating diseases are mostly lymphocytes and compound granular corpuscles, arranged in parallel rows or intermingled. Microglia cells, the histiocytes of the brain, are numerous about the areas of the exudate or are mingled with it. The presence of large mononuclear cells and epithelioid elements has also been frequently reported.

The same consistent perivascular reaction, in which lymphocytes and compound granular corpuscles predominate, has been reported with experimental anaphylaxis of the brain. In anaphylactic reactions of other organs the same perivascular reaction has been consistently noted. Large mononuclear cells and histiocytes have been reported rather constantly in cases of the advanced stages of both general and cerebral experimental anaphylaxis.

The absence or scarcity of polymorphonuclear cells in the exudate of acute demyelinating processes in the chronic stages of the process is similar to such cells in the later stages of experimental anaphylaxis. In the early stages of the reaction the exudate is formed by polymorphonuclear cells, but in the subsequent stages lymphocytes and histiocytes constitute the bulk of the cellular infiltration.

Since most of the cases of the acute demyelinating processes have been studied pathologically several days to several months after the clinical onset, and cases of the more chronic stages of disseminated and diffuse sclerosis years after the onset, it is not surprising that the lymphocytic-histiocytic type of cellular reaction dominates the picture.

Giant Cells.—The occurrence of giant cells in cases of acute disseminated encephalomyelitis or acute multiple sclerosis, as reported by various authors, constituted a feature the significance of which was obscure. This is reflected in the effort of certain investigators, such as Scherer[101] and de Lange,[102] to explain their presence in demyelinating disease on the basis of an association of a neoplastic process with multiple or diffuse sclerosis or on the basis of transitional stages between the two processes.

Now, with knowledge of the pathologic process of experimental anaphylaxis, in which the presence of giant cells and granulomatous formation is explained as an allergic reaction, one can more easily see the link between the human and the pathologic process in man and the changes induced experimentally, and is in a better position to consider the presence of giant

There seemed to be no relation between the giant cells and the severity of the damage to the tissue, inasmuch as giant cells were present not only in regions of severe involvement but in areas where only small foci of vascular reaction were noted. At times the intensity of the reaction dominated by giant cells was such as to give the impression of a tumor-like structure (fig. 23). The analogy between figures *7 A* and *B*, reproduced from Scherer,[101] and figure 23 throws light on the difficulty of interpreting certain pathologic reactions if one does not take into these experiments hemorrhages were absent, whereas hyperemia, thickening of blood vessel walls and thrombosis were still observable. On the other hand, the perivascular type of reaction was fundamentally of monocytic-histiocytic type. Indeed, my observations indicate that lymphocytes, large mononuclear cells and histiocytes form the bulk of the perivascular reaction. Here, as in the later stages of direct cerebral anaphylaxis, characteristic giant cells were also associated with a pronounced histiocytic reaction (microglia reaction). The meninges, also, though
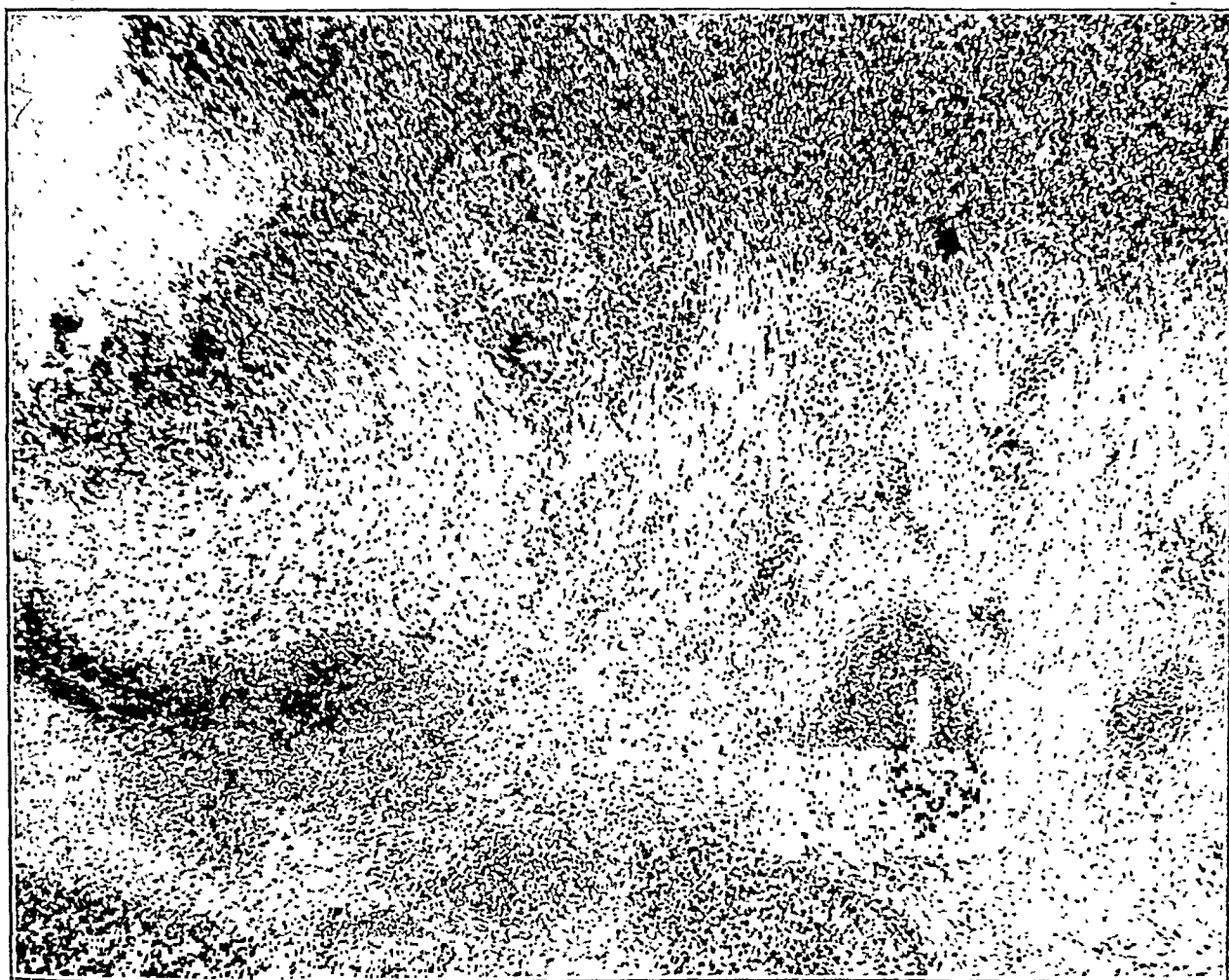
Fig. 23.—Severe perivascular reaction. In the upper part of the picture is a nodule formation, with numerous giant cells reminiscent of tumor structure. Nissl stain.

account the pathologic character of allergic reactions.

The reactions following a protracted course of intramuscular injections of brain emulsion in the monkey differ from the reactions of the acute stage of experimental cerebral anaphylaxis (Arthus phenomenon) but resemble more closely the responses observed in its advanced stages. In this connection the sensitization of the animals receiving the protracted course of injections required from a minimum of one hundred and twelve days to a maximum of four hundred and five days.

The time factor and the factor of gradual, protracted sensitization must play an important part in the variation of the histologic picture, for in to a much less pronounced degree, disclosed the presence of perivascular reaction and involvement of the blood vessel walls, similar to the response in the nerve parenchyma.

PATHOLOGIC CHARACTER OF EXPERIMENTAL
CEREBRAL ANAPHYLAXIS AS COMPARED
WITH THAT OF DEMYELINATING
DISEASE

Demyelination.—In acute disseminated encephalomyelitis, acute disseminated sclerosis and multiple and diffuse sclerosis the demyelination is chiefly perivascular. In experimental cerebral anaphylaxis demyelination is noted particularly around blood vessels.

anaphylactic reaction in the brain tissue with the histopathologic changes in the brain in 2 cases of postscarlatinal encephalitis.

In the 2 cases there was wide distribution of demyelination and perivascular reaction. The cellular elements surrounding the blood vessels were mostly lymphocytes and histiocytes. The intensity of the cellular reaction varied from one area to another, although often multilayered cuffing of lymphocytes was noticeable (fig. 24). Also, blood vessels were seen surrounded predominantly by compound granular corpuscles (fig. 25). There, also, large mononuclear cells, presumably arising from blood elements or from elements of the adventitia, occurred in the midst of a notable histiocytic reaction (fig. 26). Typical giant cells, occurring as part of a granulomatous formation, were also present in the first case (fig 8 B).

Edema, free in the tissue or more localized in the perivascular spaces of His or between the intima and the media, was also frequently encountered (fig. 27).

diseases has centered, in my opinion, around four factors: (1) a tendency on the part of investigators to create easily new clinical or pathologic entities; (2) lack of discrimination between chronic and acute pathologic changes; (3) individual tendencies to be dogmatic in interpretation of the vascular reaction and labeling of the pathologic process as inflammatory or degenerative, and (4) lack of experimental support for the establishment of a link between an acute and a chronic pathologic process on the basis of vascular reaction.

1. The tendency to create easily new clinical and clinicopathologic entities has been particularly evident in the field of the demyelinating diseases. In a tentative classification, published in 1937, I attempted to eliminate a considerable

Fig. 25—Perivascular reaction consisting chiefly of compound granular corpuscles (from Ferraro [75]). Hematoxylin and eosin stain.

Necrosis was an important feature (fig. 28). Hemorrhages were occasionally noted. Thrombi and degeneration of blood vessel walls were also present. Progressive changes in the blood vessel walls especially the adventitia and the intima, were also noted, particularly in proximity to or in the midst of necrotic areas. Proliferation of the intima resulted in considerable restriction of the lumen of the blood vessels (fig. 29).

On the basis of the analogy of these changes with the pathologic alterations of experimental anaphylaxis of the brain, I expressed the opinion that the pathologic process of postscarlatinal encephalitis could be viewed in the light of an allergic reaction.[75]

COMMENT

Up to the present the difficulty in the evaluation of the pathologic process of demyelinating

amount of confusion centered around a multitude of processes for which various names had been coined. The confusion stimulated by the creation of Schilder's disease included the diseases which bear the names of Devic, Balò, Krabbe, Foix and Alajouanine and Pelizaeus and Merzbacher.

The new nomenclature, including such terms as centrolobar sclerosis, encephaloleukopathia scleroticans, leukodystrophy, degenerative subcortical encephalopathy, leukoencephalopathy myeloclastica primitiva and encephalomyelomalacia chronica diffusa, added confusion to a point at which neither the clinician nor the neuropathologist could see his way clear.

Minimal clinical or pathologic deviations cannot, in my estimation, constitute grounds for the creation of new clinicopathologic entities when one takes into consideration the variations

cells and granulomatous reaction as an integral, though not a constant, feature of the pathologic process of demyelinating diseases.

Necrosis.—Areas of necrosis have often been reported in cases of acute multiple sclerosis and acute disseminated encephalomyelitis, as well as in cases of multiple and diffuse sclerosis. Necroses, on the other hand, are a frequent feature of experimental anaphylaxis.

one should evaluate the prominent gliosis of the chronic stages in the light of the generally long duration of the disease.

In the later stages of the anaphylactic lesion in the skin, joints or other organs, neoformation of mesodermic tissue, leading to a cicatricial process, has been reported. Jervis and I reported the occurrence of patchy gliosis with experimental cerebral anaphylaxis.
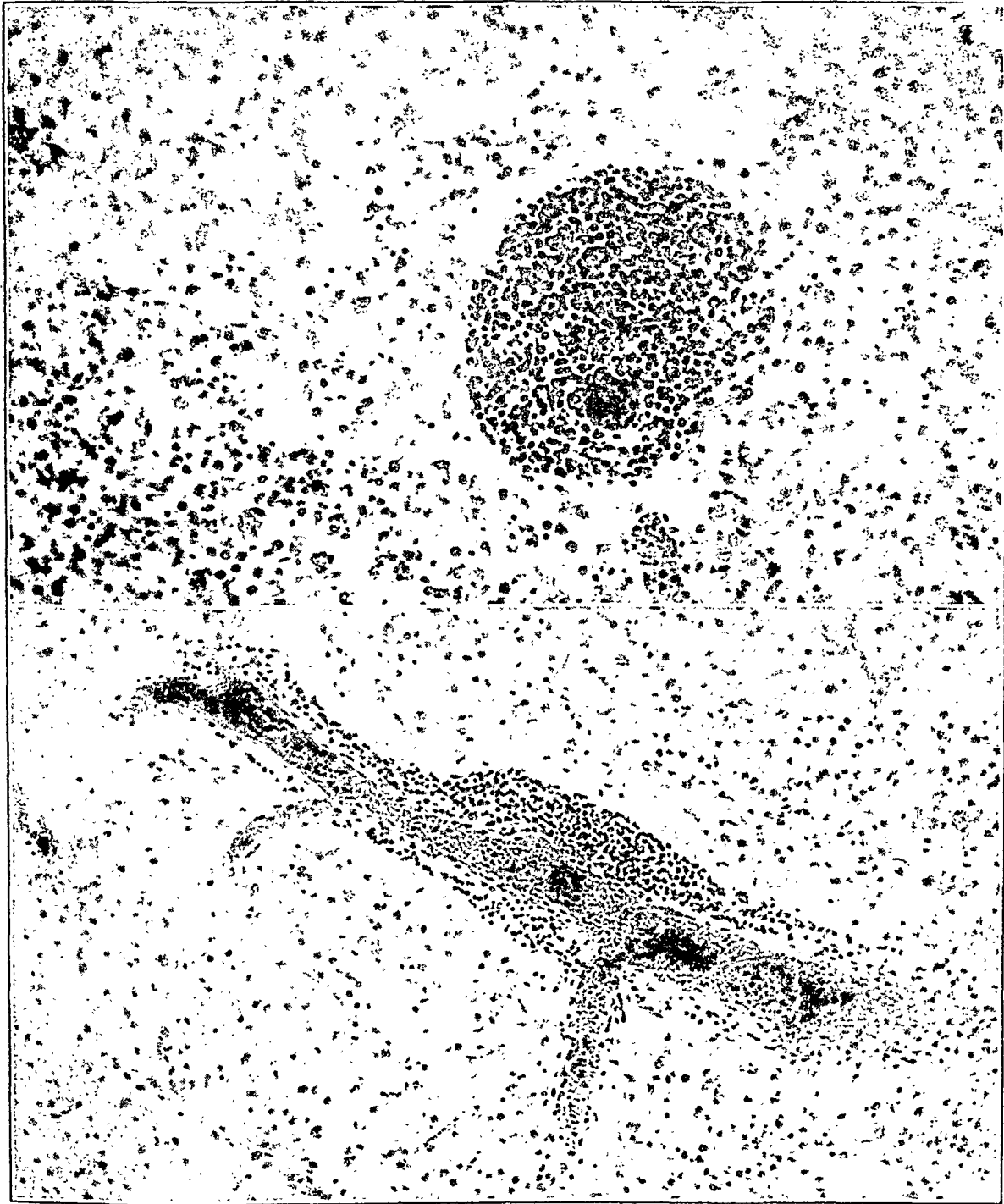
Fig. 24.—Cross and longitudinal section of blood vessels surrounded by a multilayered exudate of lymphocytes (from Ferraro [75]). Hematoxylin and eosin stain.

Repair.—Gliosis in the nervous system is in part the equivalent of the cicatricial process of repair in other organs. The patchy or diffuse gliosis (sclerosis) characteristic of the demyelinating process is generally viewed as the equivalent of such repair. One cannot expect to encounter pronounced or extensive gliosis in the acute stages of the demyelinating process, and

The similarity of the pathologic changes associated with acute and chronic demyelinating diseases and the pathologic features of experimental anaphylaxis of the brain establishes, in my opinion, a definite analogy between the two processes.

Encephalitis Complicating Scarlet Fever.— I [75] had the opportunity of comparing the aforementioned pathologic characteristics of

related to the acuteness or chronicity of the process, the age of the patient and the individual resistance of the nerve tissues. Unfortunately, these factors have often been minimized and new clinicopathologic entities soon added to express what presumably were only various aspects of the same fundamental process.

2. A second source of error in the interpretation of the pathologic features of demyelinating demyelinating disease the process is in its development, whereas in the chronic stage important transformations of some reactions, in addition to the process of repair, may have taken place.

On the other hand, one must not forget that even in the course of typical multiple sclerosis phases of reactivation may occur, expressed in terms of both clinical and pathologic exacerbation. A study of the so-called fresh areas of

Fig. 27.—Blood vessels disclosing edema between the intima and the media (from Ferraro [75]). Van Gieson stain for connective tissue.

disease has been the lack of sufficient discrimination between the acute and the chronic changes of the process. It goes without saying that the pathologic characteristics of an acute lesion may not be the same as those of the chronic lesion. Too often the difference in the pathologic features supposedly existing between an acute and a chronic demyelinating process is based on disregard of the fact that in the acute stage of demyelination which develop in the course of chronic sclerosis reveals the same histologic features observed in the acute processes of demyelination, ranging from pathologic changes of the blood vessel walls and perivascular exudate, in which both lymphocytes and compound granular corpuscles are represented, to thrombi, hemorrhages and necrosis.

Fig. 26.—Pronounced perivascular reaction, in the midst of which large mononuclear and binucleated cells are present (from Ferraro [75]). Nissl stain.

link which would permit evaluation on the basis of variations of the same process, rather than of fundamental differences. Such a link might be furnished by the studies on experimental cerebral anaphylaxis. The comparison of this pathologic process to that of demyelinating diseases suggests, in my estimation, that a common denominator in the pathologic features may be found in an allergic reaction of the nerve tissue.

The pathologic changes associated with experimental cerebral anaphylaxis briefly reported in this paper have been utilized here as a comparative standard for the evaluation of the pathologic

that the leukocytes begin to disappear as soon as a few hours after the onset of the anaphylactic reaction and that gradually the polymorphonuclear cells are substituted by lymphocytes. Practically no leukocytes are present in the later stages, when the reaction has changed, from a polymorphonuclear-hemorrhagic to a lymphocytic-histiocytic type.

In the acute, experimentally induced type of poliomyelitis the same changes occur. The exudate, which in the very early stages is formed of polymorphonuclear cells, changes into one of lymphocytes as the disease progresses. This
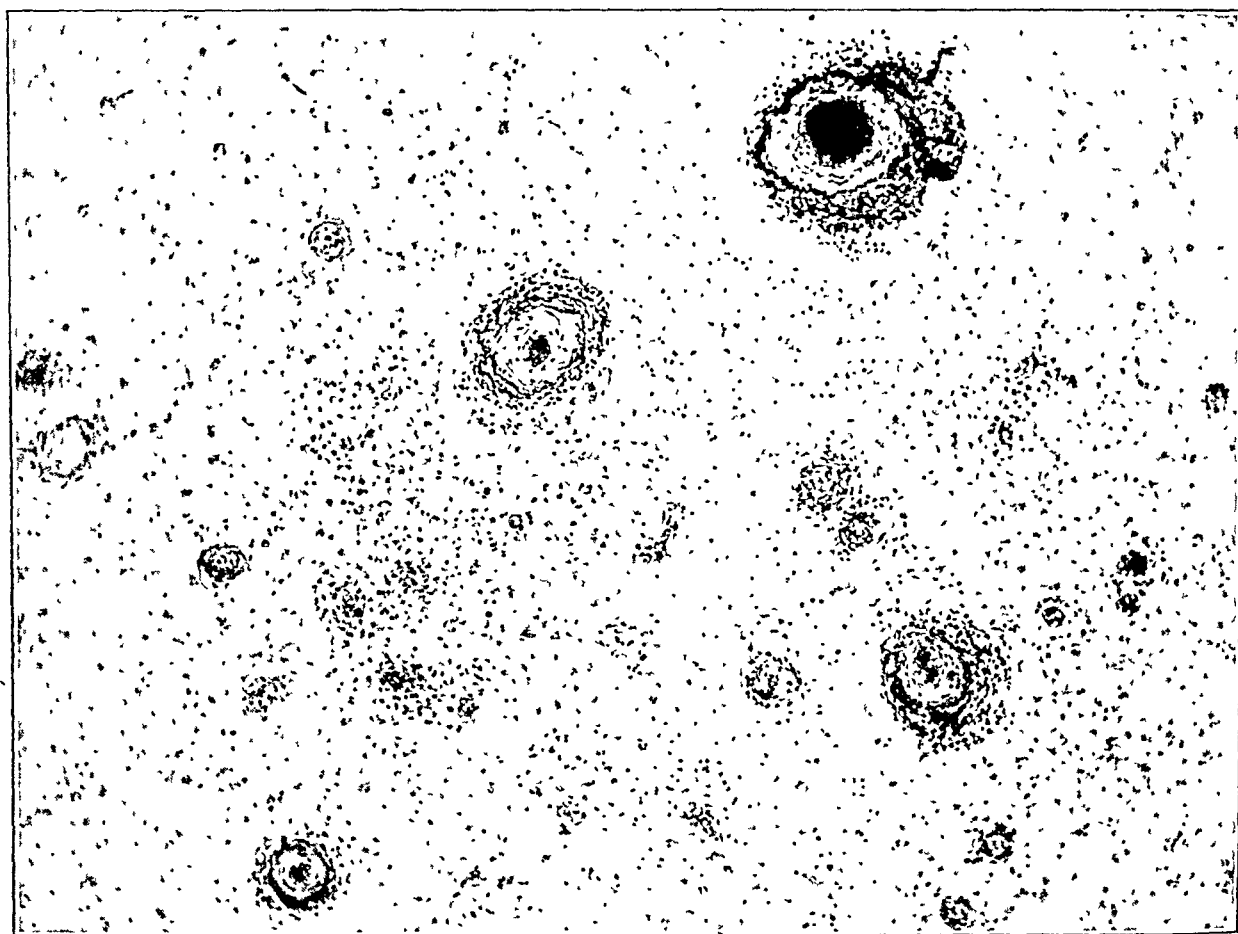
Fig. 29.—Thickening and degeneration of the blood vessel walls (from Ferraro[75]). Hematoxylin and eosin stain.

process of demyelinating disease. Emphasis has been placed on the analogy of the two conditions, with a view to establishing a possible common physiopathologic reaction.

It is true that one seldom observes with demyelinating diseases the outstanding hemorrhages typical of the Arthus phenomenon. One must, however, remember that such hemorrhages are characteristic only of the very acute and the very early stages of the reaction. It is also true that polymorphonuclear elements have rarely been reported in the perivascular exudate of demyelinating diseases, but one must remember

change in the type of exudate is important because cases of human poliomyelitis have been reported in which the exudate was formed by lymphocytes, and not by polymorphonuclear cells. But even in the absence of polymorphonuclear leukocytes, Pette[110] formulated the concept that preceding the stage of lymphocytic infiltration there presumably always is, in the severe type at least, a stage of polymorphonuclear infiltration. He, however, expressed the possibility that in cases of mild poliomyelitis the stage of leukocytic infiltration may fail to appear. In cases of acute demyelinating diseases in which

3. The third point of controversy relates to the interpretation of a pathologic process as inflammatory or degenerative. Here, again, the individual variations determined by the intensity and the duration of the pathologic process must be considered. Variations in connection with the intensity of the process are to be expected. In cases of dementia paralytica with classic symptoms microscopic examination has revealed considerable variation in the intensity of the perivascular infiltration, the amount of exudate being enormous in some cases and only moderate in others. Degenerative changes have been proved to predominate over the inflammatory changes in the juvenile form of dementia para-

in the so-called chronic stage of epidemic encephalitis is familiar to all.

One solution of the difficulty in interpretation of the presence of perivascular exudate has been to include this reaction under "symptomatic inflammation." In this term the various authors have found an escape from, rather than an explanation for, the presence of a perivascular reaction associated with a lesion of supposedly degenerative nature.

How intense this symptomatic type of perivascular reaction should be to qualify for such a label has been left entirely to the individual investigator, no satisfactory standard having been set. Thus, study of the same histologic slide by

Fig. 28.—Extensive softening and necrosis at various levels. Scarlatinal encephalitis. Gross specimens.

lytica, whereas perivascular infiltration predominates in the so-called fulminating form.

With demyelinating processes, also, one should not be surprised to find cases in which the perivascular infiltration is outstanding and others in which this feature is much less pronounced. Evidently, the question may concern the degree of intensity of the same reaction, and not different pathologic processes.

To label a process as degenerative just because the perivascular infiltration is minimal means one's losing track of the process as a whole and disregarding the important possibility that mild reactions may be dependent on the intensity of the pathologic process and on the individual tissue resistance. In addition, the age of the process must play a part in the histologic appearance of the lesion. The paucity of perivascular reaction

two different pathologists might result in the diagnosis of the same process as inflammatory by one and as degenerative by the other. On the other hand, one must keep in mind the fact that in demyelinating disease there is no parallelism between the inflammatory reaction and the intensity of the degenerative changes. The perivascular infiltration is encountered in areas in which little or no substantial degeneration of the parenchyma is noticeable, not to mention the frequent presence of exudate in the meninges in areas not related to underlying degeneration.

It is disturbing that the same reaction can be interpreted as the result of two basically different processes. Such elasticity in the interpretation of the pathologic process leading to two opposing concepts of the same process may have resulted from lack of knowledge of a possible common

As far back as 1939 Putnam and Alexander,[59b] in discussing the cause of thrombus formation in demyelinating diseases, stated:

The fact that similar "encephalomyelitides" may be provoked in animals by the injection of organ extracts and bacterial products furnishes a possible explanation for the postinfectious types. Some thrombi may be of "allergic" origin (Dietrich and Schröder, Alexander and Campbell). A great group remains, however, in regard to which there is no precise information.

In 1941 Putnam [133] again expressed the view that the origin of encephalomyelitis is in some sense an allergic reaction, adding that "it seems not unreasonable to suppose that an instability of the clotting mechanism of the blood might be one aspect of allergy."

That interference with circulation of the blood is part of the allergic reaction has been established experimentally by Doerr,[134] who reported that capillary and precapillary vessels react to anaphylactogen with changes in caliber (dilation and constriction) and with changes in permeability (edema and diapedesis).

Abell and Schenck,[71] using the transparent chamber technic devised by Clark and co-workers,[135] were able to compare the behavior of the arterioles, capillaries and venules of a normal rabbit with the corresponding vessels in the same rabbit after sensitization and injections of anaphylactogen. They observed that in a rabbit sensitized to horse serum, intravenous injection of this antigen may be followed by (a) arteriolar contraction with obliteration of the lumens of the arterioles and stoppage of the circulation, (b) increased adherence of leukocytes to the endothelium of the blood vessels and emigration of leukocytes through the walls of the capillaries and venules in large numbers and (c) sticking of leukocytes to each other to form clumps or emboli, which block the circulation in many capillaries and venules.

In addition to thrombosis, allergy may produce vascular damage in the form of periarteritis, intimal hyperplasia, fibrinoid degeneration of the intima and media (Fox and Jones [136]) and periarteritis nodosa (Vaubel,[121] Rich and Gregory [137]).

This vascular pathologic process, called hyperergic arteritis by Vaubel, and leading to reduction or occlusion of the lumen of the blood vessels, was also reported by Knepper and Waaler,[123] in an article on functional hyperactivity of the lungs and heart in the course of experimental allergy.

Vasospasm in the course of allergy was advocated by Gerlach [117] and by Knepper and Waaler,[123] and mechanical occlusion of capillaries resulting from surrounding edema was predicated by Gerlach.

It is certain that variability of the coagulation time accompanies allergic reactions. However, there seems to be a difference of opinion as to whether the coagulation time is shortened or prolonged (Urbach and Gottlieb [138]). In the so-called hemoclastic crisis of Widal, there are, for instance, decrease in the leukocyte count, relative lymphocytosis, decrease in the amount of protein colloids, lowering of blood pressure and increase in coagulability of the blood.

The unification of the pathologic changes in the brain under the heading of allergic reaction would offer a new avenue of interpretation in the field of prevention and therapy of the important group of demyelinating diseases on an immunologic basis. In this connection, Horton, Wagener, Aita and Woltman,[139] of the Mayo Clinic, have made a preliminary report of their attempts to treat multiple sclerosis, especially in the acute stage, with intravenous injections of histamine. The authors seem inclined to relate any recovery and improvement to vasodilatation in the central nervous system resulting from repeated injections of histamine. One could, however, speculate on another explanation of the beneficial effect of histamine, based on the work of Fell, Rodney and Marshall [140] and of

133. Putnam, T. J.: Newer Concepts of Postinfectious and Related Forms of Encephalitis, Bull. New York Acad. Med. 17:337-347 (May) 1941.

134. Doerr, R.: Allergische Phänomene, in Bethe, A.; von Bergmann, G.; Embden, G., and Ellinger, A.: Handbuch der normalen und pathologischen Physiologie, Berlin, Julius Springer, 1929, vol. 13, p. 650.

135. Clark, E. R.; Clark, E. L., and Williams, R. G.: Microscopic Observations in the Living Rabbit of the New Growth of Nerves and the Establishment of Nerve-Controlled Contractions of Newly Formed Arterioles, Am. J. Anat. 55:47, 1934. Clark, E. R., and Clark, E. L.: Observations on Changes in Blood Vascular Endothelium in the Living Animal, ibid. 57:385, 1935.

136. Fox, R. A., and Jones, L. R.: Vascular Pathology in Rabbits Following Administration of Foreign Protein, Proc. Soc. Exper. Biol. & Med. 55:294, 1944.

137. Rich, A. R., and Gregory, J. E.: The Experimental Demonstration That Periarteritis Nodosa Is a Manifestation of Hypersensitivity, Bull. Johns Hopkins Hosp. 72:65, 1943.

138. Urbach, E., and Gottlieb, P. M.: Allergy, New York, Grune & Stratton, Inc., 1943.

139. Horton, B. T.; Wagener, H. P.; Aita, J. A., and Woltman, H. W.: Treatment of Multiple Sclerosis by the Intravenous Administration of Histamine, J. A. M. A. 124:800 (March 18) 1944.

140. Fell, N.; Rodney, G., and Marshall, D. E.: Histamine-Protein Complexes: Synthesis and Immunologic Investation; I. Histamine-Azoprotein, J. Immunol. 47:237, 1943.

autopsy is generally performed several days after the onset of the disease, one should not be surprised at the absence of leukocytic infiltration.

As for the rest of the pathologic picture, both with anaphylaxis of the brain and with demyelinating diseases, acute or chronic, patchy or diffuse, there occur the same fundamental processes of edema, lymphatic stasis, necrosis, lymphocytic-histiocytic reaction, giant cell formation and repair.

None of these individual components of the histologic picture, taken separately, constitutes a characteristic or is pathognomonic of the anaphylactic reaction. However, evaluation of the histologic picture as a whole, with consideration for all the various components, constant or inconstant, should ultimately determine its interpretation.

It is my impression that unification of the pathologic syndrome of demyelinating diseases appears plausible as the expression of an allergic reaction of the nerve tissue. This unification has in its support the opinions expressed by investigators that from a clinical standpoint the demyelinating diseases are simply the expression of variations of the same fundamental process and the clinical impression as to their allergic nature already expressed.

The analogy of the cerebral pathology of demyelinating diseases and the pathology of cerebral anaphylaxis will open new avenues to the interpretation of the pathogenesis and histogenesis of multiple sclerosis, diffuse sclerosis and the acute encephalomyelitides.

The question arises now as to the factors responsible for the allergic reaction. The answer is difficult, especially in view of the fact that apparently different etiologic factors seem to result in the same clinicopathologic picture. The virus of vaccinia, of rabies, of measles, of influenza and of chickenpox, as well as the streptococcus of scarlet fever, all seem to bring about the same results. If one wishes to speculate on recent statements that a protein molecule constitutes the central nucleus of certain viruses, one could here find a possible explanation of the identity in type of cerebral reactions precipitated by various viruses.

On the other hand, the antigen may not necessarily originate from an infectious process. Products of intermediary metabolism could speculatively be held responsible for the production of antigens. Accurate dietary and metabolic studies in cases of demyelinating diseases might lead to the finding of additional etiologic factors, in the direction of allergic reactions rather than in that of deficiencies. The predominance of multiple sclerosis in certain geographic areas might also center around common dietary factors.

Esotoxins or endotoxins of bacteria, which are at the basis of the so-called Shwartzman phenomenon, or phenomenon of local sensitivity, may through the same mechanism result in allergic involvement of the cerebral tissue.

The importance of contributory factors in precipitating or aggravating an allergic reaction of the brain would also find its support. Some of these factors have been investigated experimentally. The contribution of Vaubel,[121] Knepper[122] and Knepper and Waaler[123] on the value of precipitating factors, such as fatigue and hyperventilation, the action of external agents, such as trauma, cold or heat, and the influence of endocrine products has demonstrated the importance of contributory factors in determining not only the intensity but the localization of the allergic reaction in certain organs.

Once the initial pathologic basis has been established in the brain, additional factors may play a role in the progress of the disease or in its phases of reactivation. I refer to the possible development of antigen (anaphylactogens) from the white or from the gray matter. The studies of Bailey and Gardner[132a] have established that antigenic substances can be derived from myelin sheaths. That the brain has immunologic properties which make that tissue almost as organ specific as the lens of the eyes is known. The brain-specific antigens, or haptens, have been claimed by some authors to have the properties of lipids only, whereas other authors (Bailey and Gardner) expressed the belief that the antigen of brain broth may be either a polysaccharide complex or a protein derivative.

Interpretation of the pathologic process of demyelinating disease on the basis of allergy could clarify the still existing confusion as to the significance of the perivascular and histiocytic reaction, so often disregarded or minimized in the study of the cerebral pathology, and might offer a common ground for evaluation of the vascular reaction as a whole under the term "hyperergic inflammation," already coined by Rossle, or of "reactive allergic inflammation," which I should like to propose.

Interpretation of the pathologic picture of demyelinating disease in the light of an allergic reaction does not exclude the histogenic origin of plaques through thrombus formation, as maintained by Putnam and his co-workers.

132a. Bailey, G. H., and Gardner, R. E.: Tissue Specificity of Brain and Medullated Nerves as Shown by Passive Anaphylaxis in the Guinea Pig, J. Exper. Med. 72:499-510 (Nov.) 1940.

THE HUMAN PYRAMIDAL TRACT

X. THE BABINSKI SIGN AND DESTRUCTION OF THE PYRAMIDAL TRACT

A. M. LASSEK, M.D., Ph.D.

CHARLESTON, S. C.

The Babinski toe sign is regarded by many clinicians as the most important superficial reflex used in neurologic diagnosis because it is thought to be indicative of destruction of the pyramidal tract. There is difference of opinion as to whether irritation of the bundle can also produce the reflex. Many physicians believe that there is scarcely a neurologic sign with less possibility of error. No matter how transient the Babinski sign, it is thought by some clinicians that it is evidence of a lesion involving the pyramidal tract and that even an equivocal sign may be regarded as of as great significance as an actual positive response.

If both irritation and destruction produce a Babinski sign, there must be diametrically opposite nervous phenomena which act on the anterior horn cells of the first sacral segment of the cord, namely, hyperactivity and hypoactivity of the pyramidal tract. According to this concept, any alteration in the conductive activity of the pyramidal tract should produce the Babinski sign. There is experimental evidence in the literature that the pyramidal tract conducts according to a pattern of so many waves per second. The following question arises: "Can interruption of the normal rhythm of pyramidal tract impulses by neurologic or systemic disease cause a physiologic block and thus a positive Babinski sign?" Physiologic block would certainly have the same effect on the cells of the lower motor neuron as loss of fibers. If this premise can be shown to be true, then one may have a sound neurologic explanation for the appearance of transient paralyses, for the instances of a brief and fluctuating Babinski sign and for the speedy functional recoveries frequently observed in medical practice which are not now adequately explained.

By definition, the pyramidal tracts consist of all the fibers which pass through the pyramids of the medulla oblongata. This definition does not take into consideration either the origin or the termination of the fibers. It is known that the pyramidal tracts have a central origin from the cerebral cortex, that they are condensed in the central portion of the internal capsules, that they course in close relation to the lateral ventricles, which frequently are affected by various degrees of internal hydrocephalus or hemorrhage and that in the brain stem and the spinal cord they are in a peripheral and exposed position. Because of these topographic relations, the pyramidal tract is probably very vulnerable to involvement by neurologic disease. It is the longest, largest and one of the most exposed tracts in the central nervous system. It is the last to develop ontogenetically and phylogenetically. The Netherland school of neurologists regards this late development of the pyramidal fasciculus as an important factor in its susceptibility to disease processes.

I believe it may be in order to assume that lesions, in some instances at least, may produce a physiologic block of pyramidal tract impulses and then to attempt to break down or confirm the hypothesis by scientific investigation. For many years the neighborhood symptoms or the remote effects of sometimes small lesions in the brain and cord have presented a baffling phenomenon, and numerous theories have been formulated to explain them.

The present paper is a summary of the evidence concerning correlation of the Babinski sign and destruction of the pyramidal tract contained in the literature, especially that published in American journals.

RESULTS

Observations with respect to the characteristics of the sign of Babinski in about 1,000 cases will be described under the following headings: (1) normal status, (2) drugs, (3) hypoglycemia, (4) sleep and narcolepsy, (5) epilepsy, (6) circulatory disturbances, (7) tumors, (8) inflammatory processes and (9) miscellaneous conditions.

Cohen and Friedman [141] on the production of histamine-specific antibodies by the use of histamine as a specific hapten conjugated by an inert protein carrier. In the experience of Fell and associates, histamine-specific antibodies were sufficient to prevent the anaphylactic shock resulting from intravenous injection of a shock-producing dose of protein. The prevention of the anaphylactic shock might be related to neutralization or destruction of the hypothetically liberated histamine. It is this explosive liberation of histamine which, according to Dale, is the cause of the anaphylactic shock.

722 West One Hundred and Sixty-Eighth Street.

141. Cohen, B. M., and Friedman, H. G.: Antibodies to Histamine Induced in Human Beings by Histamine Conjugates, J. Allergy **14**:195, 1943.

of the pancreas, or is caused by an overdose of insulin or is induced in shock therapy for schizophrenia, may produce a Babinski sign. Several hundred cases in which hypoglycemia was the factor involved occurred in the present series. The underlying mechanism in hypoglycemia appears to be a decrease in the oxygen consumption of the cerebral cortex, which results in anoxemia of the nerve tissue. The Babinski sign can be elicited prior to, during or after the period of coma; it may be transient or may last for hours or days. One patient exhibited a Babinski sign for thirteen days after hypoglycemic shock therapy. Extension of the toe may appear first on one side and then on the other. Transient hemiplegias have been described as being present for several hours.

Sleep.[4]—The Babinski sign can be elicited in normal persons during ordinary sleep or during the sleep following prolonged experimental insomnia. In young adults subjected to experimental insomnia a Babinski sign was invariably elicited on plantar stimulation in the period of sleep following the insomnia. There was not only extension but spreading of all the toes, and the reflex could be obtained any number of times provided a short period of rest was allowed between successive stimulations. On several occasions, a crossed, as well as a direct, Babinski reflex could be observed. All the tests were made without the sleeper's being wakened.

Narcolepsy and Catalepsy.[5]—A transitory Babinski sign has been reported in cases of both narcolepsy and catalepsy. An extensor response was noted in 1 patient with dementia precox who was in a catatonic state. Chronaxia studies on this patient showed. that the chronaxia during the period of elicitation of the Babinski sign was greater in the extensor than in the flexor muscle. When the Babinski sign was reversed to normal flexion on stimulation of the sole, the chronaxia of the extensor proprius muscle was less than the chronaxia of the flexor brevis muscle. This indicates a transitory modification of nerve functions associated with dementia precox which disclosed itself in a fleeting pyramidal disorder.

Epilepsy.[6]—The Babinski sign has been elicited during and after either the jacksonian or the idiopathic type of epilepsy. After the period of plantar areflexia in the attack, there is a slight extensor movement of the big toe, and eventually a classic Babinski sign appears. Monoplegia, hemiplegia and central and ocular palsy or aphasia, usually regressive, but occasionally permanent, may follow an epileptic seizure. Although the Babinski reflex cannot generally be elicited between the attacks, smaller doses of scopolamine are required to produce it than are needed for normal persons, an indication of a relative weakness or deficiency of the pyramidal tract in the epileptic patient. Sensory influence in the production of an epileptic seizure was indicated in a case in which tactile stimulation of

glycemic Treatment for Schizophrenia, Arch. Neurol. & Psychiat. **39**:853-858 (April) 1938; Biochemical Changes Occurring in the Cerebral Blood During the Insulin Treatment of Schizophrenia, J. Nerv. & Ment. Dis. **89**:273-293, 1939. Klapman, J. W., and Weinberg, M. H.: Cerebral Insult Following Hypoglycemic Shock Therapy with Recovery, Illinois M. J. **79**:236-237, 1941. Murphy, F. D., and Purtell, J.: Insulin Reaction and Brain Damage in Diabetes, Am. J. Digest. Dis. **10**:103-107, 1943. Ravid, J. M.: Transient Insulin Hypoglycemic Hemiplegias, Am. J. M. Sc. **175**:756-769, 1928. Read, C. F.; Heilbrunn, G., and Liebert, E.: Studies in the Insulin Treatment of Dementia Praecox, J. Nerv. & Ment. Dis. **90**:747-756, 1939. Reese, H. H.: Experiences with Insulin Shock Therapy in Schizophrenia, Arch. Neurol. & Psychiat. **38**:907-908 (Oct.) 1937. Reese, H. H., and Veer, A. V.: Experiences with Insulin Shock Therapy, ibid. **39**:702-716 (April) 1938. Sakel, M.: The Pharmacological Shock Treatment of Schizophrenia, translated by J. Wortis, Washington, D. C., Nervous and Mental Disease Publishing Company, 1938. Wadsworth, R. C., and McKeon, C.: Pathologic and Mental Alterations in a Case of Simond's Disease, Arch. Neurol. & Psychiat. **46**:277-296 (Aug.) 1941. Weil, A. A.: A Contribution to the "Quick-Motion-Picture" Illusion of Hoff-Pötzl, J. Nerv. & Ment. Dis. **93**:42-52, 1941. Ziskind, E.: Hyperinsulinism with Report of a Case, Arch. Neurol. & Psychiat. **26**:870-872 (Oct.) 1931.

4. Kleitman, N.: Studies on the Physiology of Sleep: I. The Effects of Prolonged Sleeplessness on Man, Am. J. Physiol. **66**:67-92, 1923. Savitsky, N., and Madonick, M. J.: Statistical Control in Neurology: I. The Sign of Babinski, Arch. Neurol. & Psychiat. **49**:272-276 (Feb.) 1943. Tournay, A.: The Babinski Sign: Its Characteristics, Mechanism and Significance, ibid. **17**:834-835 (June) 1927.

5. Jones, M. S.: A Case of Recurrent Attacks of Prolonged Sleep, J. Neurol. & Psychopath. **16**:130, 1935; abstracted, Arch. Neurol. & Psychiat. **38**:861-862 (Oct.) 1937. Redlich, E.: The Question of Narcolepsy, Ztschr. f. d. ges. Neurol. u. Psychiat. **136**:128, 1931; abstracted, Arch. Neurol. & Psychiat. **28**:173-175 (July) 1932. Wortis, S. B., and Kennedy, F.: Narcolepsy, Am. J. Psychiat. **12**:939-946, 1933.

6. Benon, R., and LeFevre, G.: A Case of Traumatic Dementia, Arch. Neurol. & Psychiat. **10**:242-243 (Aug.) 1923. Hodskins, M. B., and Yakovlev, P. I.: Neurosomatic Deterioration in Epilepsy: A Clinicopathologic Contribution to the Concept with a Report of Two Cases, ibid. **27**:113-137 (Jan.) 1932. Scarff, J. E.: Pseudojacksonian Epilepsy in Children, ibid. **49**:223-236 (Feb.) 1943. Strauss, H.: Jacksonian Seizures of Reflex Origin, ibid. **44**:140-152 (July) 1940. Tournay, A.: Behavior of the Plantar Reflex in Jacksonian Epilepsy, with Some Observations on the Pathologic Physiology of the Babinski Sign, ibid. **13**:592-595 (May) 1925. Weingrow, S. M.; Fitch, T. S. P., and Pigott, A. W.: Some Clinical Neurological Findings in Epilepsy, J. Nerv. & Ment. Dis. **88**:281-306, 1938.

Normal Status.[1]—The Babinski sign may be elicited in persons who have no other manifestations of neurologic disease. In control studies it was found that hospital patients with non-neurologic symptoms and patients with a history of head injury showed the Babinski sign in the ratio of about 4:100. On the whole, older persons were more susceptible than young ones. About 1.25 per cent of a large group of inductees between the ages of 21 and 35 exhibited the Babinski sign on proper stimulation. In severe physical exertion, such as that induced by forced marching, the Babinski sign may manifest itself in young, apparently normal, men. One observer, however, stated that the classic Babinski sign, with fanning of the toes, can never be elicited in normal persons.

Drugs.[2]—There are drugs which can either produce the sign of Babinski in normal subjects or modify it when present in diseased persons. Among the compounds found in this study which can produce the Babinski sign are nitrous oxide,

sodium amytal, barbital, general anesthetics, scopolamine, metrazol, bromide, tryparsamide and strychnine. The following report is based on several hundred cases:

Nitrous oxide produces a bilateral Babinski sign, which appears immediately after the crisis. This drug has a definite narcotic action on nerve cells, which is accentuated by anoxemia.

When sodium amytal is given intravenously, the Babinski sign can be elicited consistently just before unconsciousness occurs. This drug seems to act as an inhibitor of the activity of nerve cells, affecting the various divisions of the nervous system in the reverse order of their phylogenetic appearance. Barbital, in the same group, also produces a positive Babinski sign, especially when given in overdoses.

Scopolamine hydrobromide in doses of 0.001 Gm. may produce an extensor response in a normal person. In smaller doses, 0.0003 Gm., it brings out a latent Babinski response. This drug is a primary depressant of the central nervous system and, as such, decreases muscular tone. Physostigmine, on the other hand, abolishes the Babinski reflex. With scopolamine, extension of the big toe may last for only a few minutes, but sometimes it may remain for hours. Epileptic patients appear to be more susceptible to injections of scopolamine, an observation which may indicate a relative deficiency of the pyramidal tract in such patients.

In a few cases opium, strychnine, the general anesthetics and the bromides were reported to produce a transient Babinski sign.

Hypoglycemia.[3]— Hypoglycemia, whether it occurs spontaneously, as the result of an adenoma

1. Davison, H. A.: Plantar Reflexes in Normal Adults, Arch. Neurol. & Psychiat. **26**:1027-1037 (Nov.) 1931. Savitsky, N., and Madonick, M. J.: Statistical Control Studies in Neurology: I. The Sign of Babinski, ibid. **49**:272-276 (Feb.) 1943. Yakovlev, P. I., and Farrell, M. J.: Influence of Locomotion on the Plantar Reflex in Normal and in Physically and Mentally Inferior Persons: Theoretic and Practical Implications, ibid. **46**:322-330 (Aug.) 1941.

2. Courville, C. B.: Asphyxia as a Consequence of Nitrous Oxide Anesthesia, Medicine **15**:129-245, 1936. Curran, F. J.: A Study of Fifty Cases of Bromide Psychosis, J. Nerv. & Ment. Dis. **88**:163-192, 1938. Delgado, H.: Treatment of Schizophrenia with Cardiazol in Convulsant Doses, ibid. **89**:625-639, 1939. Finkelman, I.; Steinberg, D. L., and Liebert, E.: Treatment of Schizophrenia with Metrazol by Production of Convulsions, J. A. M. A. **110**:706-709 (March 5) 1938. Gyárfás, K.: Correlations of Athetosis, Catatonia and Hypoglycemia, J. Nerv. & Ment. Dis. **87**:588-597, 1938. Hodskins, M. B., and Yakovlev, P. I.: Neurosomatic Deterioration in Epilepsy, Arch. Neurol. & Psychiat. **23**:986-1031 (May) 1930. Lichtenstein, B. W.: Acute and Subacute Toxic Myelopathies Following Therapy with Arsphenamines, ibid. **48**:740-760 (Nov.) 1942. Low, A. A.; Sonenthal, I. R.; Blaurock, M. F.; Kaplan, M., and Sherman, I.: Metrazol Shock Treatment of the "Functional" Psychoses, ibid. **39**:717-736 (April) 1938. Marinesco, G., and Nicolesco, M.: Modifications of Postural Tonus with Babinski Sign After Injections of Scopolamine in Extrapyramidal Hypertonia, Rev. neurol. **1**:246-249, 1927. Pamboukis, G., and Tsiminakis, J.: Cardiazol Treatment in Schizophrenia, Encéphale **2**:94-103, 1938; abstracted, J. Nerv. & Ment. Dis. **96**:717-718, 1942. Purves-Stewart, J.: Cisternal and Lumbar Drainage in the Treatment of Coma from Acute Barbital Poisoning, Together with Observations on Chronic Barbital Poisoning, Jahrb. f. Psychiat. u. Neurol. **51**:203-213, 1934. Thorner, M. W.: The Psycho-pharmacology of Sodium Amytal, J. Nerv. & Ment. Dis. **81**:161-167, 1935. Tournay, A.: The Babinski Sign: Its Characteristics, Mechanism and Significance, Arch. Neurol. & Psychiat. **17**:834-835 (June)

1927. von Thurzo, E.: Ueber einige neuere diagnostische und therapeutische Verfahren in der Neurologie, Berlin, S. Karger, 1929. Zador, J.: Conditions Affecting and the Pathogenesis of the Babinski Reflex, Monatschr. f. Psychiat. u. Neurol. **64**:336, 1927; abstracted, Arch. Neurol. & Psychiat. **20**:847-848 (Oct.) 1927.

3. Bassoe, P., and Traut, E.: The Neurologic Manifestations of Insulin Reactions, Arch. Neurol. & Psychiat. **21**:238-240 (Jan.) 1929. Feinier, L.: Neuropsychiatric Symptomatology in a Case of Hypoglycemia, ibid. **32**:1350-1353 (Dec.) 1934. Fortuyn, J. D.: Hypoglycemia and the Autonomic Nervous System, J. Nerv. & Ment. Dis. **93**:1-15, 1941. Freed, H., and Saxe, E.: Prolonged Nonhypoglycemic Coma Occurring During the Course of Insulin Shock Therapy, ibid. **90**:216-226, 1939. Frostig, J. P.: Insulin Therapy of Schizophrenia, Schweiz. Arch. f. Neurol. u. Psychiat. **39**:153-157, 1938. Greenwood, J.: A Case of Psychosis Due to Hypoglycemia, Arch. Neurol. & Psychiat. **33**:232-234 (Feb.) 1935. Heiman, M.: Significance of Babinski Sign During Hypoglycemic Treatment of Schizophrenia, Am. J. Psychiat. **96**:387-391, 1939. Himwich, H. E.; Bowman, K. M.; Wortis, J., and Fazekas, J. F.: Brain Metabolism During the Hypo-

bundle can be affected by the blood stream in many other ways than by hemorrhage, thrombosis or embolism of vessels within the central nervous system.

Acute massive hemorrhage or chronic loss of blood in any portion of the body may apparently cause paralytic symptoms, with the Babinski sign. This reflex has been reported in cases of gastric hemorrhage, hemorrhoids, hemoptysis of the lungs and postpartum hemorrhage. Blood transfusion alleviates the paralysis and reverses the extensor toe reflex to the normal response in the early stages. Sometimes hemiplegia may not make itself evident for as long as thirty-six hours after the onset of the hemorrhage. Prolonged bleeding, however, may produce permanent damage. A red blood cell count of approximately 2,000,000 or lower, is mentioned as being the critical level below which paralysis, with the Babinski sign, may appear.

Hemiplegia, with a Babinski sign, has been reported in persons with extremely low blood pressure. It is believed that in such cases the blood is not pumped adequately to the cerebral cortex, which creates anoxemia in the brain.

Temporary circulatory arrest produced the Babinski sign in 2 of 10 cases, but it could not be induced a second time. Cerebral air embolism has been described as producing temporary paralysis and the Babinski sign. In some instances the air may be absorbed before any permanent motor deficit is in evidence.

Too many red blood cells, as in polycythemia or leukemia, or too few, as in the secondary anemias or in pernicious anemia, may produce the Babinski sign. Abnormal cell types, such as are present in sickle cell anemia or malaria, likewise may cause anoxemia of the brain, with a resultant

Babinski sign. Changes in the oxygen–carbon dioxide–combining power of the hemoglobin, such as those associated with carbon monoxide poisoning or Cheyne-Stokes respiration, can produce a temporary Babinski sign.

An oversensitive carotid sinus reflex has been observed to cause periodic temporary hemiplegia, with the Babinski sign. In the hands of some clinicians, denervation has mitigated the defects. Section of the cervical sympathetic fibers in a patient with hemiplegia was followed by recovery, including the disappearance of the pathologic Babinski reflex.

Free blood in the subarachnoid space due to ruptured cerebral aneurysm, or from other causes, will in some instances cause temporary hemiplegia, with the Babinski sign. This is usually explained as due either to an irritating effect of the blood or to pressure. Blood when present on the convex surface of the cerebral cortex supposedly acts on the so-called motor cortex, whereas when present on the base of the brain it is thought to produce its effects by acting on the exposed pyramids of the medulla. Blood in the form of hematoma must produce its paralytic effects mainly by pressure. When the blood is removed, either in the free state or in the form of hematoma, recovery from all symptoms often occurs. Spontaneous recovery also may follow subarachnoid bleeding. Hemorrhage or blocked accumulations of cerebrospinal fluid in the lateral ventricles evidently produce a Babinski sign by pressure on the pyramidal tract fibers as they pass through the internal capsule.

Acute swelling of the brain or edema may also cause paralytic signs and symptoms, among which is the Babinski sign. On subsidence of the edema, the signs disappear in many cases. Neighborhood or contralateral effects are frequently explained on this basis, the latter occurring especially in the brain stem and the spinal cord. The transient Babinski reflex observed in cases of lobotomy or anterior chordotomy can be best defended on the basis of this phenomenon.

Tumors.[8]—Certain patients with tumor of the central nervous system who had classic signs

O. R., and King, A. B.: Apraxia: Report of a Case with Autopsy, ibid. **48**:469-475 (Sept.) 1942. Tournay, A.: Cheyne-Stokes Respiration and Periodic Babinski Sign, ibid. **18**:652 (Oct.) 1927. Tournay, A., and Holtzhauser, R.: Posterolateral Sclerosis Following Massive Hemorrhage, ibid. **29**:1368-1369 (June) 1933. Tureen, L. L.: Lesions of the Fundus Associated with Brain Hemorrhage, ibid. **42**:664-678 (Oct.) 1939. Urechia, C. I.: Pseudotumor Syndrome Dependent on Acute Swelling of the Brain, Rev. neurol. **27**:1185, 1920; abstracted, Arch. Neurol. & Psychiat. **8**:696-697 (Dec.) 1922. Watts, J. W., and Freeman, W.: Psychosurgery: Effect on Certain Mental Symptoms of Surgical Interruption of Pathways in the Frontal Lobe, J. Nerv. & Ment. Dis. **88**:589-601, 1938. Wertham, F.; Mitchell, N., and Angrist, A.: The Brain in Sickle Cell Anemia, Arch. Neurol. & Psychiat. **47**:752-767 (May) 1942. Wetherell, F. S.: Cervicodorsal Sympathectomy in Multiple Sclerosis: Its Rationale and Report of Eight Cases, ibid. **34**:99-110 (July) 1935. Winkelman, N. W., and Eckel, J. L.: Brain Trauma: Histopathology During the Early Stages, ibid. **31**:956-986 (May) 1934.

8. Allen, S. S., and Lovell, H. W.: Tumors of the Third Ventricle, Arch. Neurol. & Psychiat. **28**:990-1006 (May) 1932. Alpers, B. J., and Groff, R. A.: Parasellar Tumors: Meningeal Fibroblastomas Arising from the Sphenoid Ridge, ibid. **31**:711-736 (April) 1934. Alpers, B. J., and Yaskin, J. C.: Gliomas of the Pons: Clinical and Pathologic Characteristics, ibid. **41**:435-459 (March) 1939. Andersen, C.: Cushing's Syndrome: Hypophysial Basophilism, J. belge de neurol. et de psychiat. **35**:148, 1935; abstracted, Arch. Neurol. & Psychiat. **36**:423 (Aug.) 1936. Aronson, L.: Clinical Report of a Case of Intramedullary Neoplasm of

the skin or mucous membrane on any part of the right side of the body initiated a jacksonian attack with a Babinski sign. During periods of improvement the Babinski sign disappeared.

Circulatory Disturbances.[7]—There is abundant evidence in the literature that the pyramidal

7. Abbott, K. H.: Amnesic Aphasia Due to Two Small Focal Lesions, Bull. Los Angeles Neurol. Soc. **3:** 188-190, 1938. Ahrens, R. S.: Neurologic Aspects of Primary Anemia, Arch. Neurol. & Psychiat. **28:**173-175 (July) 1932. Allison, R. S., and Morison, J. E.: Cerebral Vascular Lesion and the Tentorial Pressure Cone, J. Neurol. & Psychiat. **4:**1-10, 1941. Alpers, B. J.: Ventricular Hemorrhage with Recovery: Report of a Case, Arch. Neurol. & Psychiat. **12:**695-700 (Dec.) 1924. Austregesilo, A.: Nervous Disorders in Certain Tropical Diseases, Rev. neurol. **1:**1-21, 1927; abstracted, Arch. Neurol. & Psychiat. **18:**596-599 (Oct.) 1927. Bagley, C.: Spontaneous Cerebral Hemorrhage, ibid. **27:**1131-1174 (May) 1932. Burley, B. T.: Two Cases of Cerebral Hemorrhage in Young Adults, ibid. **9:**803-807 (June) 1923. Cohen, I.: Chronic Subdural Accumulations of Cerebrospinal Fluid After Cranial Trauma: Report of a Case, ibid. **18:**709-723 (Nov.) 1927. Cooper, M. J.: Transient Hemiplegia in a Syphilitic Patient of Twenty-Eight, ibid. **28:**218-221 (July) 1932. Courtney, J. W.: Case of Myelitis of Unusual Etiology, ibid. **18:**482-485 (Sept.) 1927. Dimitri, V.: Superior Alternating Hemiplegia, Rev. Asoc. méd. argent. **53:**1109-1113, 1939. Dohan, F. C.: A Case of Occlusion of the Sylvian Artery, Arch. Neurol. & Psychiat. **29:**1369-1370 (June) 1933. Freedberg, A. S., and Sloan, L. H.: Association of Carotid Sinus Reflexes with Syncope and Convulsions, ibid. **38:**761-774 (Oct.) 1937. Globus, J.: Probable Topographic Relations of the Sleep-Regulating Center, ibid. **43:**125-138 (Jan.) 1940. Gordon, A.: Painful Hemiplegia: A Consideration of Central Pain, ibid. **38:**211-214 (July) 1937. Griffith, J. Q.: Involvement of the Facial Nerve in Malignant Hypertension, ibid. **29:**1195-1202 (June) 1933. Hadden, S.: Neurological Symptoms in Posthemorrhagic Secondary Anemia, Ann. Int. Med. **9:**1572-1577, 1936. Hadden, S., and Wilson, G.: Objective Symptoms of Involvement of the Spinal Cord in Cases of Pernicious Anemia Removed with Treatment, Arch. Neurol. & Psychiat. **36:**888-890 (Oct.) 1936. Hyland, H. H.: Thrombosis of Intracranial Arteries: Report of Three Cases Involving, Respectively, the Anterior Cerebral, Basilar and Internal Carotid Arteries, ibid. **30:**342-356 (Aug.) 1933. Hyland, H. H., and Farquharson, R. F.: Subacute Combined Degeneration of the Spinal Cord in Pernicious Anemia, ibid. **36:**1166-1205 (Dec.) 1936. Hyndman, O.: Physiology of the Spinal Cord: I. Role of the Anterior Column in Hyperreflexia, ibid. **46:**695-703 (Oct.) 1941; II. Influence of Chordotomy on Existing Motor Disturbances, J. Nerv. & Ment. Dis. **98:**343-358, 1943. Hyndman, O., and Wolkin, J.: Anterior Chordotomy: Further Observations on Physiologic Results and Optimum Manner of Performance, Arch. Neurol. & Psychiat. **50:**129-148 (Aug.) 1943. Jefferson, G.: Bilateral Rigidity in Middle Meningeal Hemorrhage, Brit. M. J. **2:**683-685, 1921. Kampmeier, R. H.: Sickle Cell Anemia as a Cause of Cerebral Vascular Disease, Arch. Neurol. & Psychiat. **36:**1323-1329 (Dec.) 1936. King, A. B., and Langworthy, O. R.: Neurologic Symptoms Following Extensive Occlusion of the Common or Internal Carotid Artery, ibid. **46:**835-842 (Nov.) 1941. Krabbe, K. H.: Facial and Meningeal Angio-

matosis Associated with Calcifications of the Brain Cortex, ibid. **32:**736-755 (Oct.) 1934. Leopold, S. S.: Ruptured Aneurysm at Junction of Right Anterior Communicating and Anterior Cerebral Arteries, ibid. **31:**605-610 (March) 1934. Levinson, A.: Acute Transitory Cerebral Manifestations in Infants and in Children, J. A. M. A. **101:**765-770 (Sept. 2) 1933. Lhermitte, J., and Trelles, J. O.: Physiology and Physiopathology of the Corpus Striatum and Subthalamic Region, Encéphale **27:**235-271, 1932; abstracted, Arch. Neurol. & Psychiat. **29:**874-876 (April) 1933. McConnell, A. A.: Intracranial Conditions After Closed Head Injuries, Brain **65:**266-280, 1942. McGovern, F. H.: Cerebral Air Embolism Following Antral Irrigation, Arch. Otolaryng. **34:**593-595 (Sept.) 1941. Pilcher, C.: Subcortical Hematoma: Surgical Treatment, with Report of Eight Cases, Arch. Neurol. & Psychiat. **46:**416-430 (Sept.) 1941. Priest, W. M.: Epidural Hemorrhage Due to Hemophilia Causing Compression of the Spinal Cord, Lancet **2:**1289, 1935; abstracted, Arch. Neurol. & Psychiat. **37:**1189 (May) 1937. Putnam, T. J.: Section of the Extrapyramidal Tracts in the Treatment of Dystonia Musculorum Deformans, ibid. **28:**208-210 (July) 1932. Quincke, H.: Acute Circumscribed Edema and Related Conditions, Med. Klin. **17:**675, 1921; abstracted, Arch. Neurol. & Psychiat. **6:**682-684 (Dec.) 1921. Rangell, L.: Cerebral Air Embolism, J. Nerv. & Ment. Dis. **96:**542-555, 1942. Reider, N.: Neuropsychiatric Complications Following Severe Loss of Blood, Arch. Neurol. & Psychiat. **44:**1069-1075 (Nov.) 1940. Remond, A., and Colombies, H.: Hemiplegia with Hemichorea, Rev. de méd. **39:**107, 1922; abstracted, Arch. Neurol. & Psychiat. **9:**103-104 (Jan.) 1923. Romano, J., and Evans, J. W.: Symptomatic Psychosis in a Case of Secondary Anemia, Arch. Neurol. & Psychiat. **39:**1294-1301 (Dec.) 1938. Rossen, R.; Kabat, H., and Anderson, J. P.: Acute Arrest of Cerebral Circulation in Man, ibid. **50:**510-528 (Nov.) 1943. Sands, I. J.: Aneurysm of the Right Posterior Communicating Artery of the Circle of Willis Producing the Syndrome of Alternating Oculomotor Hemiplegia, ibid. **14:**554-558 (Oct.) 1925; Aneurysm of Cerebral Vessels: Clinical and Pathologic Presentation, ibid. **19:**732-734 (April) 1928; Aneurysms of the Cerebral Vessels, ibid. **21:**37-46 (Jan.) 1929. von Sarbó, A.: Aneurysms of the Dura Mater, ibid. **22:**1-4 (July) 1929. Scott, M.: Trigemino-Auricular Reflex, ibid. **43:**181-182 (Jan.) 1940. Shallow, T., and Burns, M. A.: A Case of Thrombosis of the Vertebral, Basilar and Internal Carotid Arteries, ibid. **31:**455-458 (Feb.) 1934. Sherman, I. C., and Krumholz, S.: A Case of Intradural Hematoma with Ipsilateral Hemiplegia and Ipsilateral Third Nerve Palsy, J. Nerv. & Ment. Dis. **95:**176-182, 1942. Steiner, G.: Chronic Perivascular Demyelination (Homophasic Cerebrospinal Demyelinating Periangiosis), Arch. Neurol. & Psychiat. **41:**166-178 (Jan.) 1939. Stephenson, J. W.: Disappearance of Tremor in a Case of Paralysis Agitans Following an Attack of Hemiplegia, with Comments on the Production of the Tremor in Paralysis Agitans, ibid. **23:**199-201 (Jan.) 1930. Stief, A.: A Case of Hemiatrophy of the Face with Autopsy Observations, Ztschr. f. d. ges. Neurol. u. Psychiat. **147:**573, 1933; abstracted, Arch. Neurol. & Psychiat. **31:**1107-1108 (May) 1934. von Stockert, F. G.: A Case of Bilateral Occlusion of the Posterior Cerebral Artery, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **34:**23, 1932; abstracted, Arch. Neurol. & Psychiat. **30:**1372-1373 (Dec.) 1933. Strauss, I.; Globus, J. H., and Ginsburg, S. W.: Spontaneous Subarachnoid Hemorrhage, ibid. **27:**1080-1132 (May) 1932. Teitelbaum, H. A.; Langworthy,

of involvement of the pyramidal tract were selected for the following reasons: (1) because they had recovered from signs and symptoms referable to the pyramidal tract after surgical removal of the mass or after roentgen ray treatment or (2) because the tumor appeared to produce its effect although located at some distance from the known site of the pyramidal tract.

The pyramidal tract appears to be highly susceptible to effects of pressure, even of a slight degree. Extramedullary tumors which produced the Babinski signs have been removed from every·part of the central nervous system, their removal being followed by loss of the reflex. These areas include the forepart of the frontal lobe and the parietal, occipital and temporal lobes, as well as the cavum septum pellucidi, the medulla oblongata, the cerebellum, the cerebellopontile angle, the filum terminale below the conus medullaris of the spinal cord and the pituitary and pineal glands. Most of the extramedullary tumors in this series were removed from the spinal cord. Speedy recovery was reported in some cases. Even in cases of long standing, when pressure is relieved there may be quick functional .return of movements and disappearance of the Babinski sign. Apparently, few studies have been made on the correlation of pressure of the tumor on nerve tissue, destruction of the pyramidal tract and recovery. The indications thus far are that pressure on the cord in some cases causes local demyelination, without evidence of degeneration above or below the lesion. Obviously, more studies of this nature are needed before final conclusions can be formulated. For example, I have noted four different explanations as to why cerebellar lesions may cause a Babinski sign; they implicate respectively four parts of the central nervous system, namely, the cerebrum, the mesencephalon, the medulla oblongata and the upper part of the spinal cord. Each one of the explanations is not supported by scientific proof, as far as I have been able to determine.

Autopsy observations also support the view that remote tumor lesions can produce signs referable to the pyramidal tract. Here, again, tumors in every part of the nervous system, as well as extramedullary tumors, have been mentioned. Sometimes small tumorous lesions, remotely situated, may produce classic pyramidal

signs, and various attempts to explain this phenomenon have been made. Edema, circulatory disturbance, anoxemia and increased intracranial pressure have been suggested in an attempt to clarify this occurrence. It may be mentioned that in some instances the pyramidal tract has appeared normal when studied post mortem.

One of the interesting features of the present study was the frequent occurrence of a bilateral Babinski sign with unilateral space-consuming lesions.

Inflammatory Processes.[9]—A variety of inflammatory processes may produce a transient

9. Alexander, M. E., and Allen, H. E.: Lethargic Encephalitis: A Report of Four Cases and an Analysis of One Hundred Cases Reported in the Literature, ibid. **3**:485-499 (May) 1920. Alfandary, I., and Stayitch, S.: Papillary Stasis in Encephalitis, Rev. d'oto-neuro-opht. **12**:503, 1934; abstracted, Arch. Neurol. & Psychiat. **33**:866-867 (April) 1935. Arnold, J. G.: Primary Ependymitis: Subacute Type with Occlusion of the Foramina of Monro and Hydrocephalus of the Lateral Ventricles, ibid. **32**:143-153 (July) 1934. Atkinson, M.: Localized Nonsuppurative Encephalitis Adjacent to a Focus of Infection in the Skull, ibid. **41**:556-564 (March) 1939. Beckmann, J. W.: Neurologic Aspects of the Epidemic of Encephalitis in St. Louis, ibid. **33**:732-751 (April) 1935. Bernstein, M.: The Hemiplegic Form of Epidemic Encephalitis: Report of a Case with Recovery, ibid. **13**:139-141 (Jan.) 1925. Brock, S., and Ivimey, M.: Toxic-Infectious Disease in the Peripheral and Central Nervous System —So-Called Neuronitis, ibid. **19**:129-141 (Jan.) 1928. Brouwer, B.: Arachnoiditis Adhesiva Circumscripta, ibid. **30**:639-644 (Sept.) 1933. Burr, C. W.: Typhoid Fever Apparent Exciting Cause of Cerebrospinal Symptoms of Syphilis, ibid. **14**:572-574 (Oct.) 1925. Cohen, I.: Justifications for and Results of Exploratory Laminectomy, ibid. **24**:373-380 (Aug.) 1930; Metastatic Abscess of the Brain: Operation; Recovery, ibid. **25**:910-912 (April) 1931. Courville, C. B., and Nielsen, J. M.: Otogenous Abscess of the Parietal Lobe, Bull. Los Angeles Neurol. Soc. **1**:65-70, 1936. Davidoff, L. M., and Dyke, C. G.: Series of Cases of Serous Meningitis, Arch. Neurol. & Psychiat. **36**:1376-1380 (Dec.) 1936. Davis, D. B., and Currier, F. P.: Forced Grasping and Groping, ibid. **26**:600-607 (Sept.) 1931. Davison, C., and Kelman, H.: Combined System Disease in Tabes Dorsalis, ibid. **38**:43-61 (July) 1937. Diamond, I. B., and Bassoe, P.: Abscess of the Brain: Report of Two Cases—One with the Clinical Picture of Epidemic Encephalitis and the Other with That of Tumor of the Brain, ibid. **19**:265-280 (Feb.) 1928. Gill, J. C., and Richter, R.: Encephalitis Disseminata: A Clinical and Anatomic Report of a Case with Features Akin to Multiple Sclerosis and Diffuse Sclerosis, ibid. **28**:1072-1090 (May) 1932. Gilpin, S. F.: A Patient with Myoclonus Following Epidemic Encephalitis, ibid. **5**:222-223 (Feb.) 1921; A Patient with Myelitis and Neuritis, ibid. **7**:142-143 (Jan.) 1922. Gorter, E.: Postvaccinal Encephalitis, J. A. M. A. **101**:1871-1873 (Dec. 9) 1933. Hassin, G. B.: Syphilis of the Oculomotor Nerve, Arch. Neurol. & Psychiat. **25**:116-127 (Jan.) 1931. Kaplan, A.: Abscess of the Brain: Recovery Following the Use of the Mosher Drain, ibid.

Rev. d'oto-neuro-opht. **9**:571, 1931; abstracted, Arch. Neurol. & Psychiat. **28**:197 (July) 1932. Warren, J. V., and Romano, J.: Spinal Epidural Granuloma: Report of a Case, ibid. **48**:789-798 (Nov.) 1942. Yaskin, J. C.: Homolateral Involvement of the Pyramidal Tract in Cerebral Tumors, ibid. **22**:1024-1028 (Nov.) 1929.

the Spinal Cord; Operation; Deep X-Ray Therapy; Marked Improvement, ibid. **21**:233-235 (Jan.) 1929. Bailey, P., and Oldberg, E.: An Unusual Tumor of the Cerebellum: Report of a Case, ibid. **48**:149-150 (Dec.) 1942. Bogaert, L. V.: The Thalamic and Parkinsonian Types of Infundibular Tumors: The Occurrence of Glycoregulatory and So-Called Endocrine Disorders, ibid. **19**:377-393 .(March) 1928. Burns, M. A.: Relative Value of Diagnostic Measures in the Localization of Tumors of the Brain, ibid. **20**:627-634 (Sept.) 1928. Courville, C. B.: Ganglioglioma: Tumor of the Central Nervous System; Review of the Literature and Report of Two Cases, ibid. **24**:439-491 (Sept.) 1930; Gangliogliomas: A Further Report with Special Reference to Those Occurring in the Temporal Lobe, ibid. **25**:309-326 (Feb.) 1931. Cushing, H., and Ayer, J. B.: Xanthocromia and Increased Protein in the Spinal Fluid Above Tumors of the Cauda Equina, ibid. **10**:167-193 (Aug.) 1923. Dandy, W. E.: Congenital Cerebral Cysts of the Cavum Septi Pellucidi (Fifth Ventricle) and Cavum Vergae (Sixth Ventricle), ibid. **25**:44-66 (Jan.) 1931. Denker, P. G., and Osborne, R. L.: Aberrant Thyroid Tumor of the Vertebrae with Compression of the Spinal Cord: Recovery After Operation and High Voltage Roentgen Therapy, ibid. **49**:277-281 (Feb.) 1943. Ecker, A.: Removal of Tumor Arising Anterior to the Medulla, ibid. **46**:908-912 (Nov.) 1941. Elsberg, C. A.: The False Localizing Signs of Spinal Cord Tumor, ibid. **5**:64-79 (Jan.) 1921. Elsberg, C. A., and Globus, J. H.: Tumors of the Brain with Acute Onset and Rapidly Progressive Course, ibid. **21**:1044-1078 (May) 1929. Elsberg, C. A., and Strauss, I.: Tumors of the Spinal Cord Which Project into the Posterior Cranial Fossa, ibid. **21**:261-273 (Feb.) 1929. Favill, J.: Two Specimens of Occipital Lobe Lesions, ibid. **10**:115-118 (July) 1923. Fay, T.: Vasomotor and Pilomotor Manifestations: Their Localizing Value in Tumors and Lesions of the Spinal Cord; a Report of Thirteen Verified Cases, ibid. **19**:31-46 (Jan.) 1928; A Case of Gumma of the Brain with Onset of Symptoms Following Trauma: Operative Removal with Recovery, ibid. **22**:169-170 (July) 1929. Ferber, L., and Lampe, I.: Hemangioma of Vertebra Associated with Compression of the Cord, ibid. **47**:19-29 (Jan.) 1942. Frazier, C. H., and Spiller, W. G.: An Analysis of Fourteen Consecutive Cases of Spinal Cord Tumor, ibid. **8**:455-501 (Nov.) 1922. Frazier, C. H., and Alpers, B. J.: Meningeal Fibroblastomas of the Cerebrum: A Clinicopathologic Analysis of Seventy-Five Cases, ibid. **29**:935-989 (May) 1933. Friedman, E. D.: Lesion of the Upper Cervical Portion of the Cord, Resembling Combined System Disease: Presentation of a Case, ibid. **37**:430-435 (Feb.) 1937. Gardner, W. J.: Tumor of. the Spinal Cord Associated with Bilateral Acoustic Tumors, ibid. **24**:1014-1022 (Nov.) 1930. Gill, J. C.: A Specimen of Tumor of the Brain, ibid. **20**:414-415 (Aug.) 1928. Globus, J. H., and Strauss, I.: Spongioblastoma Multiforme: A Primary Malignant Form of Brain Neoplasm; Its Clinical and Anatomic Features, ibid. **14**:139-191 (Aug.) 1925; Intraspinal Iodolography: Subarachnoid Injection of Iodized Oil as an Aid in the Detection and Localization of Lesions Compressing the Cord, ibid. **21**:1331-1386 (June) 1929. Globus, J. H., and Meltzer, T.: Metastatic Tumors of the Brain, ibid. **48**:163-226 (Aug.) 1942. Gould, E. M.: Tumors of the Posterior Cranial Fossa: Homolateral and Contralateral Pyramidal Tract Signs, ibid. **19**:509-514 (March) 1928. Grant, F. C.: The Successful Removal of Tumors of the Brain and of the Spinal Cord, ibid. **20**:634-638 (Sept.) 1928. Gross, S. W.: Cerebral

Arteriography: Its Place in Neurologic Diagnosis, ibid. **46**:704-714 (Oct.) 1941. Hall, G. W., and Hirsch, E. F.: Paraplegia in Flexion, with Subacute, Combined Degeneration of the Cord, ibid. **23**:257-265 (Feb.) 1930. Helfand, M.: Status Pigmentatus: Its Pathology and Its Relation to Hallervorden-Spatz Disease, J. Nerv. & Ment. Dis. **81**:662-675, 1935. Horrax, G., and Bailey, P.: Pineal Pathology: Further Studies, Arch. Neurol. & Psychiat. **19**:394-414 (March) 1928. Kennedy, F.: Symptomatology of Frontal and Temporosphenoidal Tumors, J. A. M. A. **98**:864-866 (March 12) 1932. Kernohan, J. W., and Woltman, H. W.: Incisura of the Crus Due to Contralateral Brain Tumor, Arch. Neurol. & Psychiat. **21**:274-287 (Feb.) 1929. Keschner, M., and Davison, C.: Myelitic and Myelopathic Lesions: V. Compression of the Spinal Cord by Expanding Lesions Producing Mild, Moderate or Marked Interference with the Circulation Leading to Myelopathy, ibid. **30**:592-606 (Sept.) 1933. Lassek, A. M.: The Human Pyramidal Tract: IX. Effect of Paralysis Produced by Cerebral Tumors on Axons of Pyramids, ibid. **51**:213-215 (March) 1944. Naffziger, H. C., and Brown, H. A.: Hour-Glass Tumors of the Spine, ibid. **29**:561-584 (March) 1933. Ody, F.: Tumors of the Basal Ganglia, ibid. **27**:249-269 (Feb.) 1932. Pilcher, C.: Spongioblastoma Polare of the Pons: Clinicopathologic Study of Eleven Cases, ibid. **32**:1210-1229 (Dec.) 1934. Raeder, O. J.: Osteoma of the Spinal Arachnoid with Psammomatous Degeneration, ibid. **21**:1079-1086 (May) 1929. Sachs, E.; Rose, D. K., and Kaplan, A.: Tumor of the Filum Terminale, with Cystometric Studies: Report of Two Cases, ibid. **24**:1133-1153 (Dec.) 1930. Sands, I. J.: A Case of Pituitary Tumor with Coma Followed by Complete Recovery, ibid. **18**:461-462 (Sept.) 1927; Diagnosis and Management of Subarachnoid Hemorrhage, ibid. **46**:973-1005 (Dec.) 1941. Scarff, J. E.: Spastic Hemiplegia in an Infant Produced by a Congenital Cyst Entirely Replacing the Cerebellar Vermis, ibid. **31**:205 (Jan.) 1934. Schick, W.: Tumor High in the Cervical Region of the Spinal Cord Simulating Combined System Disease, ibid. **32**:1343-1345 (Dec.) 1934. Schlesinger, B.: Syndrome of the Fibrillary Astrocytomas of the Temporal Lobe, ibid. **29**:843-854 (April) 1933. Schnitker, M. T., and Ayer, D.: The Primary Melanomas of the Leptomeninges: A Clinicopathologic Study with a Review of the Literature and the Report of an Additional Case, J. Nerv. & Ment. Dis. **87**:45-73, 1938. Schwarz, G. A., and Rosner, A. A.: Displacement and Herniation of the Hippocampal Gyrus Through the Incisura Tentorii: A Clinicopathologic Study, Arch. Neurol. & Psychiat. **46**:297-321 (Aug.) 1941. Sellheim, A. P.: Tumor of the Brain in the Monkey, J. belge de neurol. et de psychiat. **36**:240, 1936; abstracted, Arch. Neurol. & Psychiat. **38**:154 (July) 1937. Silverstein, A.: Cerebral Muscular Atrophy as a Significant Sign of Tumor of the Parietal Lobe with Presentation of Cases, ibid. **26**:670-674 (Sept.) 1931. Silverstein, A., and Winkelman, N. W.: A Case of Cerebellopontile Angle Tumor Showing Unusual Symptomatology: A New Operative Approach, ibid. **23**:838-841 (April) 1930. Spiller, W. G.: An Enchondroma of the Brain Removed with Recovery, ibid. **9**:536-538 (April) 1923. Stevenson, L., and Echlin, F.: Nature and Origin of Some Tumors of the Cerebellum: Medulloblastoma, ibid. **31**:93-109 (Jan.) 1934. Stone, L., and Menninger, W. C.: A Case of Psychosis Associated with Midline Cerebellar Tumors, ibid. **33**:399-405 (Feb.) 1935. Vincent, C.; Roger, H., and Giraud, M.: Olfactory Meningioma,

Babinski sign are (1) hyperthermia, (2) cortical inferiority, (3) congenital or acquired atrophy, (4) unexplained demyelination, (5) cerebral calcification, (6) hepatolenticular degeneration, (7) Ascaris ova in the intestine, (8) hypercholemia, (9) uremia and (10) chronic masturbation. In 1 case the Babinski sign seemed to have a functional basis. The sign may be abolished by application of an Esmarch bandage on the leg, by a cold foot bath and by administration of physostigmine. A hot foot bath, as well as small quantities of scopolamine, elicits a latent Babinski sign. The position of the head on the body also modifies the reflex.

COMMENT [11]

For many years it has been thought that the sign of Babinski results only from destruction of the pyramidal tract. A permanent Babinski sign, according to this view, is produced only on complete loss of pyramidal fibers. The question arises as to why total disappearance of neurons is required to produce this lasting effect. Anatomically, it can mean only one thing, namely, that the axons which are destined for the first sacral segment, the part of the cord concerned with the Babinski reflex, must be scattered throughout the entire area of the pyramidal tract. If this is true, there is no localization of fibers within the tract. Further, the duration of the Babinski sign must be proportional to the amount of fiber loss. I am not sure that this thesis can be defended scientifically. Recovery, whether spontaneous or following surgical removal, and remote effects from space-consuming lesions are sometimes difficult to explain on this basis, especially in cases in which no diminution of pyramidal fibers is noted post mortem. With respect to the sign of Babinski, I believe that the effects of cortical ablations or experimental lesions in other portions of the central nervous systems in the chimpanzee or monkey cannot be compared or correlated too closely with the reflex which occurs in diseased conditions in man. Perhaps all the neurologic diseases which affect man cannot be simulated by application of the scalpel, cautery, suction apparatus or electrolytic instruments to the central nervous system of other primates. For example, whereas it required widespread cortical damage in the monkey (hemidecortication and ablation of the thalamus) to produce the sign of Babinski, the reflex was easily elicited in a monkey with a tumor confined to the occipital lobe.

On analysis of about 1,000 cases the actual and circumstantial evidence appears to be overwhelming that the sign of Babinski can be exhibited without any fibers of the pyramidal tract being destroyed. Cases in which this occurred formed a fairly high percentage of the total number studied, and they may, therefore, be of sufficient importance to be taken seriously in the diagnosis of neurologic diseases.

(March) 1933; Parenchymatous Cortical Cellebellar Atrophy (Subacute Cerebellar Encephalitis), ibid. **33:** 959-975 (May) 1935. Patrick, H. T.: The Symptoms of Lhermitte in Multiple Sclerosis, ibid. **23:**1075-1077 (May) 1930. Patten, C. A.: Cerebral Birth Conditions, with Special Reference to Cerebral Diplegia, ibid. **25:** 453-468 (March) 1931. Riley, H. A., and Brock, S.: Rhythmic Myoclonus of the Muscles of the Palate, Pharynx, Larynx and Other Regions: A Clinical Report of Three Cases, ibid. **29:**726-741 (April) 1933. Shearer, C.: A Case of Functional Epileptiform Seizure with Babinski Reflex, Lancet **1:**1322, 1925. Strecker, E. A.; Taft, A. E., and Willey, G. F.: Mental Sequelae of Carbon Monoxide Poisoning, with Reports of Autopsy in Two Cases, Arch. Neurol. & Psychiat. **17:**552-554 (April) 1927. Thomas, J. J.: Report of a Case of Cervical Syringomyelia, ibid. **6:** 98-99 (July) 1921. Verhaart, W. J. C.: An Unclassified Degenerative Disease of the Central Nervous System, ibid. **44:**1262-1270 (Dec.) 1940. Waggoner, R. W.; Löwenberg, K., and Speicher, K. G.: Hereditary Cerebellar Ataxia, ibid. **39:**570-586 (March) 1938. Yaskin, J. C.: Injury of One Pyramidal Tract Resulting from a Knitting Needle Puncture Wound of the Cervical Region of the Cord, ibid. **9:**413-414 (March) 1923. Yaskin, J. C., and Wilson, G.: Case of Traumatic Psychosis in a Child, ibid. **37:**201-205 (Feb.) 1937.

11. Cobb, S.: Causes of Epilepsy, Arch. Neurol. & Psychiat. **27:**1245-1263 (May) 1932. Dandy, W. E.: The Brain, in Lewis, D.: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1944, vol. 12, chap. 1. Filimonoff, I. N.: Nature of the So-Called Pathologic Reflexes, Ztschr. f. d. ges. Neurol. u. Psychiat. **103:**416-434, 1926. Forster, F. M., and Campbell, J. B.: The Sign of Babinski in Macaca Mulata, J. Nerv. & Ment. Dis. **96:**493-498, 1942. Fulton, J. F., and Viets, H. R.: Upper Motor Neuron Lesions: Analysis of Syndromes of Motor and Premotor Areas, J. A. M. A. **104:**357-362 (Feb. 2) 1935. Goldflam, S.: Die diagnostische Bedeutung des Rossolimoschen Reflex bei Erkrankungen des Zentralnervensystems: Eine klinischanatomische Studie, Berlin, S. Karger, 1930, p. 274. Goldstein, K.: The Sign of Babinski, J. Nerv. & Ment. Dis. **93:**281-296 (March) 1941. Keschner, M., and Grossman, M.: Cerebellar Symptomatology Evaluation on the Basis of Intracerebral and Extracerebellar Lesions, Arch. Neurol. & Psychiat. **19:**78-94 (Jan.) 1928. Langworthy, O. R.; Highberger, E., and Foster, R.: Hemiplegia with the Leg in Flexion, ibid. **34:** 520-532 (Sept.) 1935. Orton, S.: A Theory of the Genesis of Tremor in Lenticular Disease, ibid. **23:**183-187 (Jan.) 1930. Spiller, W. G.: Hyperreflexia of Lower Limbs After Exercise, J. A. M. A. **87:**639-640 (Aug. 28) 1926. Tournay, A.: The Babinski Sign: Its Characteristics, Mechanism and Significance, Arch. Neurol. & Psychiat. **17:**834-835 (June) 1927. Zador, J.: Conditions Affecting the Pathogenesis of the Babinski Reflex, Monatschr. f. Psychiat. u. Neurol. **64:**336-349, 1927; abstracted, Arch. Neurol. & Psychiat. **20:** 847-848 (Oct.) 1928.

Babinski sign, among which have been mentioned the following conditions: various forms of encephalitis (optic, nonsuppurative, serous, postvaccinal, disseminated, epidemic and lethargic encephalitis and acute benign meningoencephalitis), uveoparotid fever, otogenous abscess, epidemic parotitis, arachnoiditis adhesiva circumscripta, influenza, syphilis, tetanus, typhoid, radiculomyelitic syndrome, neuronitis, cerebellar abscess, abscess of the cord, myelitis complicating varicella, actinomycosis and myelitis. The terminology here used is that employed by the authors. In many cases the transient Babinski response and paralytic signs were followed by complete recovery. In some instances the investigators were unable to find any evidence of damage to the pyramidal tract at autopsy. The puzzling role of edema in manifestations of neurologic deficiencies has been discussed by some authors. Surgical drainage of abscess in this series has frequently been followed, sometimes rapidly, by disappearance of symptoms and signs referable to the pyramidal tract. One patient presented notable evidence of a transverse lesion of the cord, which was followed by recovery, including disappearance of the Babinski sign.

Miscellaneous Conditions.[10] — Other conditions reported in the literature as producing the

33:667-673 (March) 1935. Kennedy, F.: Acute Benign Meningo-Encephalitis with Papilledema, ibid. **7:**53-57 (Jan.) 1922; Acute Intracranial Edema Complicating Otitis Media, ibid. **27:**1497-1499 (June) 1932; Encephalomyelitis Optica: Report of a Case, ibid. **48:**855-857 (Nov.) 1942. Keschner, M., and Sloane, P.: Encephalitic, Idiopathic and Arteriosclerotic Parkinsonism: A Clinicopathologic Study, ibid. **25:**1011-1041 (May) 1931. Klemmer, R. N.: A Case of Actinomycosis of the Cerebrum, ibid. **10:**479-480 (Oct.) 1923. Krabbe, K. H.: Varicella Myelitis, Brain **48:**535-539, 1925. Levin, P. M.: The Neurological Aspects of Uveoparotid Fever, J. Nerv. & Ment. Dis. **81:**176-191, 1935. McKaig, C. B., and Woltman, H. W.: Neurologic Complications of Epidemic Parotitis: Report of a Case of Parotitic Myelitis, Arch. Neurol. & Psychiat. **31:**794-808 (April) 1934. Nielsen, J. M.: Symptomatology of Otogenic Abscess of the Temporal Lobe, ibid. **29:**676-678 (March) 1933. Rabiner, A. M.: Radicular and Radiculomyelitic Syndromes with Recovery, ibid. **21:**224-226 (Jan.) 1929. Strauss, I., and Rabiner, A. M.: Myeloradiculitis: A Clinical Syndrome, with Report of Seven Cases, ibid. **23:**240-256 (Feb.) 1930. Woltmann, H. W., and Adson, A. W.: Abscess of the Spinal Cord: Report of a Case with Functional Recovery After Operation, Brain **49:**193-206, 1926. Zimmerman, H. M., and Yannet, H.: Nonsuppurative Encephalomyelitis Accompanying Chickenpox, Arch. Neurol. & Psychiat. **26:**322-332 (Aug.) 1931.

10. Abraham, A. E., and Baird, J. A.: Clinical and Subclinical Lead Intoxication, War Med. **2:**450-453 (May) 1942. Akelaitis, A. J. E., and Garvey, P. H.: Acute Demyelinizing Processes in the Nervous System, J. Nerv. & Ment. Dis. **94:**405-427, 1941. Alpers, B. J., and Dear, R. B.: Hemiatrophy of the Brain, ibid. **89:**

653-671, 1939. Arnheim, E. E.: A Case of Toxemia Presenting Unusual Clinical Manifestations, with Recovery, Arch. Neurol. & Psychiat. **16:**369 (Sept.) 1926. Babcock, C. G., and Brosin, H. W.: Hepatolenticular Degeneration: Report of a Case, ibid. **46:**431-439 (Sept.) 1941. Becker, F.: Triplegia Appearing Eighteen Years After an Injury of the Head and Greatly Benefited by Operation, ibid. **13:**660-661 (May) 1925. Benedek, L.: The Babinski Response in Eclampsia, Lancet **1:**1322, 1925. Bragman, L. J.: Reflexes in Amyotonia Congenita (Oppenheim): Report of a Case with Signs of Involvement of the Pyramidal Tract, Arch. Neurol. & Psychiat. **31:**161-163 (Jan.) 1934. Brock, S., and Wolf, A.: Cerebral Complications of Icterus Gravis Neonatorum, ibid. **36:**1368-1372 (Dec.) 1936. Bury, J. S.: The Significance of Some Early Symptoms of Nervous Disease, Lancet **2:**549-551, 1921. Cadwalader, W. B.: The Condition of a Patient in Good Health, but Exhibiting Automatic Movements of the Lower Limbs, Nineteen Years After Complete Transverse Section of the Spinal Cord by a Gunshot Wound, Arch. Neurol. & Psychiat. **4:**108-111 (July) 1920. Elliott, T. R., and Walshe, F. M. R.: The Babinski or Extensor Form of Plantar Response in Toxic States, Apart from Organic Disease of the Pyramidal Tract System, Lancet **1:**65-68, 1925. Frazier, C. H., and Ingham, S. D.: A Review of the Effects of Gunshot Wounds of the Head, Arch. Neurol. & Psychiat. **3:**17-40 (Jan.) 1920. Freedom, L.: Cerebral Birth Palsies: A Contribution to Their Pathology with a Report of a Hitherto Undescribed Form, ibid. **26:**524-548 (Sept.) 1931. Furui, R.: The Pathology of Compression of the Spinal Cord, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **29:**169, 1927; abstracted, Arch. Neurol. & Psychiat. **19:**348-350 (Feb.) 1928. Goldensohn, L. N.; Clardy, E. R., and Levine, K.: Agenesis of the Corpus Callosum, J. Nerv. & Ment. Dis. **93:**567-580, 1941. Goldstein, K., and Katz, S. E.: The Psychopathology of Pick's Disease, Arch. Neurol. & Psychiat. **38:**473-490 (Sept.) 1937. Gordon, A.: Familial Muscular Atrophy, ibid. **30:**460-462 (Aug.) 1933. Gordon, R. G., and Norman, R. M.: Further Observations on Neurological Abnormalities in Mental Defectives, J. Neurol. & Psychiat. **1:**173-179, 1938. Gurdjian, E. S., and Schlafer, N. H.: Fracture of the Skull with Injury of the Brain, Arch. Neurol. & Psychiat. **26:**583-592 (Sept.) 1931. Hassin, G. B.: Concussion of the Spinal Cord: A Case with the Clinical Picture of Amyotrophic Lateral Sclerosis, ibid. **10:**194-211 (Aug.) 1923. Hausman, L., and Bromberg, W.: Diabetic Exophthalmic Dysostosis, ibid. **21:**1402-1420 (June) 1929. Irish, C. W.: Presentation of a Case of Posttraumatic Psychosis with Mental Deterioration, ibid. **34:**1347-1349 (Dec.) 1935. Kasanin, J., and Crank, R. P.: A Case of Extensive Calcification in the Brain: Selective Calcification of the Finer Cerebral Blood Vessels, ibid. **34:**164-178 (July) 1935. Löwenberg, K.; Boyd, D. A., and Salon, D. D.: Occurrence of Pick's Disease in Early Adult Years, ibid. **41:**1004-1020 (May) 1939. Marcovitz, E., and Alpers, B. J.: The Central Nervous System in Mushroom Poisoning, ibid. **33:**53-71 (Jan.) 1935. Matthews, R., and McDade, R.: Neurologic Conditions in Three Hundred and Nine Mentally Defective Children, ibid. **29:**668 (March) 1933. Noica, D., and Radovici, A.: Abolition of the Babinski Sign by Cold and Its Reappearance After Heat, Rev. neurol. **26:**891, 1919; abstracted, Arch. Neurol. & Psychiat. **5:**330-331 (March) 1921. Parker, H. L., and Kernohan, J. W.: Stenosis of the Aqueduct of Sylvius, ibid. **29:**538-560

baths tend to bring out a latent Babinski sign, whereas cold water has the opposite effect. Scopolamine in minute quantities brings out a latent Babinski sign and with administration of larger amounts a Babinski sign can be elicited in normal persons; physostigmine has the opposite effect.

An interesting feature noted in the study was the frequent occurrence of a bilateral Babinski sign with a unilateral lesion. This was especially true of space-consuming masses in the cerebrum. It is realized that this phenomenon has been explained in a few instances by the shifting of the brain mass so that the opposite cerebral peduncle comes in contact with the tentorium cerebelli. Shifting of the pyramids of the medulla against the border of the foramen magnum has also been mentioned as a possible explanation for the phenomenon. Although this explanation may suffice in some cases, I feel that it may not be the only one and that further investigation is in order. In order to determine the cause of a bilateral Babinski effect in such cases, one must first be sure of all the factors involving production of the reflex on one side.

I wish to emphasize that it is not intended to imply that the conditions which have been enumerated and discussed in this article always produce a Babinski sign with paralytic symptoms. The cases in this series are selected; they were chosen because in some manner they gave evidence against the view that the Babinski sign and destruction of the pyramidal tract go hand in hand. Further search would unquestionably bring to light many additional pertinent cases, perhaps thousands, in support of the essential observations reported here. A monograph, at least, could be written on the subject if the evidence were comprehensively reviewed.

CONCLUSIONS

1. The evidence appears to be overwhelming that the sign of Babinski can be elicited in persons with no loss of pyramidal tract fibers.

2. A small percentage of persons without any manifestations of neurologic disease may exhibit the Babinski sign on proper stimulation.

3. A temporary sign of Babinski can be produced in normal subjects under various conditions, as follows: (a) severe exertion; (b) subjection to the action of depressant drugs; (c) spontaneous or induced hypoglycemia; (d) deep sleep; (e) blood disorders; (f) ingestion of certain toxic chemicals or poisonous gases, and (g) many miscellaneous conditions.

4. Many systemic or neurologic inflammatory diseases may cause a transient or fluctuating Babinski sign.

5. Pressure on the pyramidal tract almost invariably produces an extensor toe response, which may disappear when the cause of the pressure is removed. In some of the cases in this series no signs of descending degeneration in the pyramidal tract were apparent at autopsy.

6. Remote space-consuming lesions may produce a sign of Babinski through edema, anoxemia or other phenomena.

7. The mechanism involved in producing the sign of Babinski in disease conditions in man may be of a capricious nature.

Department of Anatomy, Medical College of the State of South Carolina.

It is difficult to find a common denominator to explain the production of a Babinski sign in cases without loss of fibers in the pyramids. If the pyramidal tract is concerned at all in the pathogenesis of this neurologic sign, then there are certain factors or phenomena which constantly appear in many cases, such as anoxemia, pressure, circulatory disturbance, edema, augmented cerebrospinal pressure and constitutional weakness of the pyramidal neurons. It is logical to assume that physiologic block of impulses mediated by the pyramidal tract would have the same effect on the lower motor neuron as does loss of fibers. The question therefore arises as to whether any of the phenomena of neurologic disease mentioned can produce a physiologic block of impulses conducted by the pyramidal tract. Any analysis must consider the pyramidal neuron from its beginning to its termination because it apparently is vulnerable throughout its entire extent.

Probably the most defensible explanation of a possible physiologic block of pyramidal conduction is that embodied in the broad term "depression of nerve activity." Any one of the phenomena mentioned, i. e., anoxemia, pressure edema, circulatory disturbance or increased intracranial pressure, might conceivably have a depressant effect on the pyramidal tract fibers. The various drugs mentioned are described, for the most part, as having an inhibitory effect on the cortical cells. There may be cortical inhibition during sleep, in narcoleptic and cataleptic attacks and on physical exertion, all of which have been accompanied by signs of involvement of the pyramidal tract without destruction. Anoxmeia, whether it is caused by hypoglycemia, loss of blood, temporary circulatory arrest, air embolism, polycythemia, oligocythemia, an oversensitive carotid sinus reflex, Cheyne-Stokes respiration, carbon monoxide poisoning or other factors, may cause a depression of nerve activity in the pyramidal tract.

Pressure of space-consuming lesions on the pyramidal tract might easily block descending nerve impulses. Some unusual cases of motor recovery are reported in the literature when such a mass has been removed by operation or controlled by roentgen irradiation. The few clinico-pathologic investigations that have been made in this respect indicate that the pathologic changes consist largely of local demyelination without descending or ascending degeneration. Such observations are consistent with the speedy recoveries reported. On the other hand, one report states that in general the pathologic changes were in agreement with the clinical symptoms.

Many observers have been at a loss to describe the remote or the neighborhood effects of certain lesions, especially tumors. In cases of such lesions, spreading edema or circulatory disturbance is described repeatedly, and in some instances the pyramidal tract has appeared normal at autopsy. On the basis of this study, it is difficult to neglect edema as a causative factor in the production of a Babinski sign. The pressure of tumors or other space-consuming lesions on blood vessels might create a partial anoxemic condition in the areas surrounding the tumor mass. It is interesting that lobotomy and anterior chordotomy, involving narrow incisions made at some distance from the known region of the pyramidal tracts, may cause a transient Babinski sign. Edema probably best explains this reaction.

Inflammation, through the elimination of toxins by bacteria, might conceivably exert a depressant effect on the nerve cells or the fibers constituting the pyramidal tract. The toxins which may be prevalent in cases of the hepatic insufficiencies, uremia, Ascaris infestation of the intestine and the unexplained myelitic processes may be placed in this category.

The role of some miscellaneous conditions which produce the Babinski sign is difficult to explain. Among these conditions may be mentioned hyperthermia, cortical inferiority, congenital atrophy and masturbation. Cortical inferiority is probably the easiest of these factors to discuss. There must be great individual variation in the stability of the pyramidal tract, since it certainly is not cast in any standard mold. Persons with a relatively weak pyramidal system and with poor power of transmission might exhibit the Babinski sign, whereas persons with a more durable system would not. Studies on apparently young normal persons and on mentally defective and epileptic subjects indicate that this may be true. I cannot offer any suggestions as to why the Babinski sign should be associated with chronic masturbation. Further observations are undoubtedly necessary. The 1 case cited in which the Babinski sign appeared to be due to a functional disturbance should probably not be accepted without further confirmation; an overwhelming mass of evidence is against the elicitation of a Babinski sign on a functional or a hysterical basis.

That the Babinski sign may be modified in a number of ways suggests that the integrity of the peripheral nerves is important. An Esmarch bandage on the leg abolishes the reflex, and the position of the head on the body has altered the sign in the hands of some observers. Hot foot

or closely adjacent groups of muscle fibers discharging repetitively.

An increase in the number of spontaneous muscle movements could always be produced by extension of the fingers. In C of the figure some of these synchronous contractions were recorded from the abductor digiti quinti muscle after stretch of the fifth finger. In this tracing one group of muscle fibers is seen to discharge at a rate of 8 to 10 per second; soon a much larger wave of potentials passes the electrodes at about the same frequency, while the first continues. The pattern of these discharges was regular. They tended to appear in constant rhythmic groups, which were repeated at intervals over a long period. For instance, groups of three to four discharges at a rate of 8 to 10 per second might constitute the rhythm, with variable periods of inactivity between. After several minutes, with the finger extended, the large synchronous bursts

nerves were stimulated on the involved side with the recording electrodes placed over the muscles which were the seat of the spontaneous activity. In no instance was there any detectable response after stimulation of the motor nerve, although the amplification used was sufficient to record with ease the spontaneous discharges.

As an additional means of excluding nerve discharges as the basis of these synchronized movements, the muscles were "curarized" by the injection of 200 mg. of β-erythroidine hydrochloride into the brachial artery. As soon as the injection was completed, the venous blood flow was momentarily obstructed by the application of a pressure cuff (40 mm. of mercury) proximal to the point of injection. The effectiveness of the injection in blocking nerve-muscle transmission was easily demonstrated. Electrodes were connected with the thenar eminence, and muscle action potentials
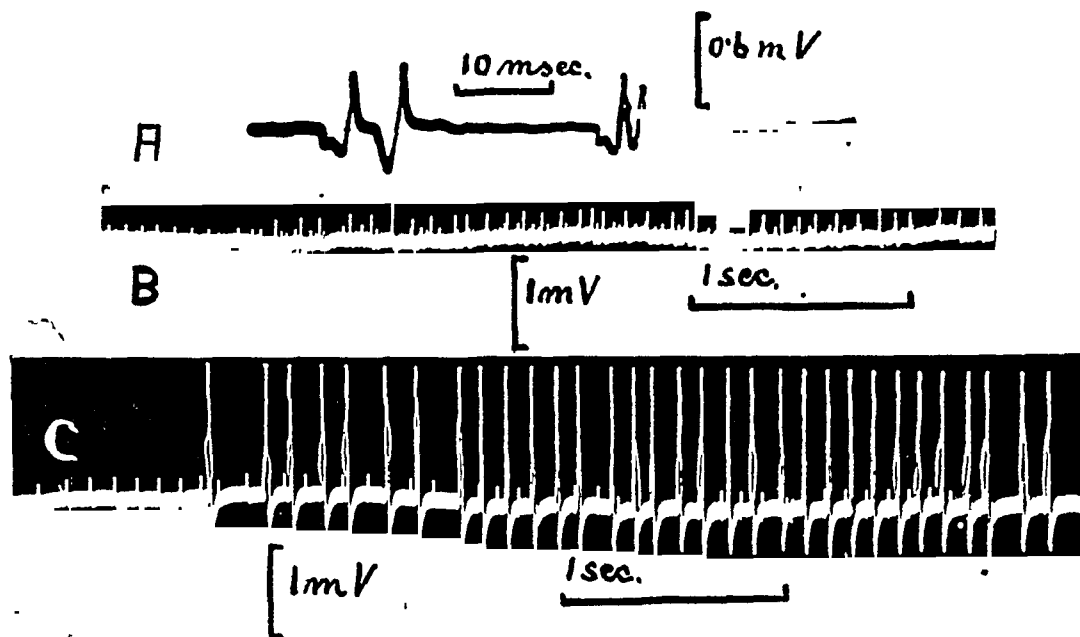
A and *B,* muscle action potentials of spontaneous activity recorded from abductor digiti quinti muscle. *A* shows potentials recorded with a cathode ray oscillograph, and *B,* activity recorded on the slowly moving film of an electrocardiograph. *C,* muscle activity recorded on an electrocardiograph from the abductor digiti quinti muscle after stretch of the fifth finger.

disappeared gradually, and the muscle returned slowly to the level of activity which existed before the stretch. Apparently, accommodation to the stretch stimulus occurred.

The important feature of these muscle movements was their appearance in muscles which had no apparent innervation. Although the nerve which supplied these muscles had been completely divided at operation, and no voluntary movement was evident, it seemed necessary to obtain additional proof that these unusual synchronized movements were initiated in muscle fibers which were deprived of any functioning nerve fibers.

It was first necessary to exclude the possibility of innervation by fibers from another nerve. The median, radial and ulnar nerves of the normal arm were stimulated electrically and the action potentials recorded from appropriate areas. The strength of the stimulus necessary to produce a maximal response of the muscle to both single and repetitive nerve impulses was determined. With stimuli the strength of which was at least 30 per cent greater than this, the corresponding

characteristic of voluntary movements of the thumb were recorded prior to the injection. For four to five minutes after the injection voluntary movement of the thumb was not possible, and during that time no action potentials could be recorded from the thenar eminence.

However, the spontaneous discharges from the muscles of the hypothenar eminence persisted with the same frequency and showed the usual increase in number when the muscles were stretched. It seems clear from these observations that the responses arose in muscle fibers which had been deprived of any motor innervation.

The grouping and rhythmicity of these discharges were similar to those described by Adrian and Gelfan[4] in frog muscle in the presence of a deficiency of calcium following the application of sodium citrate. One gram of calcium gluconate was given intravenously, and the contractions were recorded electrically before and after

4. Adrian, E. D., and Gelfan, S.: Rhythmic Activity in Skeletal Muscle Fibers, J. Physiol. **78**:271, 1933.

SYNCHRONIZATION OF SPONTANEOUS ACTIVITY IN DENERVATED HUMAN MUSCLE

MAJOR ABNER M. HARVEY

MEDICAL CORPS, ARMY OF THE UNITED STATES

AND

STEPHEN W. KUFFLER

RESEARCH FELLOW, KANEMATSU MEMORIAL INSTITUTE OF PATHOLOGY, SYDNEY HOSPITAL

SYDNEY, AUSTRALIA

If mammalian muscle is deprived of its nerve supply, no spontaneous activity can be observed for several days. After that period spontaneous contraction of individual muscle fibers sets in, and may persist for a year or longer unless nerve regeneration occurs or the contractile muscle tissue disappears.[1] This activity is not visible through the skin. Visible movements of groups of muscle fibers are always associated with the discharge of at least one motor nerve impulse.[2] To our knowledge, there has not been described in the literature a case of spontaneous synchronized activity of muscle fibers in a completely denervated muscle. Such a case, in which absence of innervation could be ascertained by various methods, has been under observation for several months at an Army general hospital.

REPORT OF A CASE

Clinical History.—A white man aged 24 entered the hospital Sept. 10, 1943, because of paralysis of the left ulnar nerve. He had been in an automobile accident in November 1940, at which time a small splinter of glass entered the medial surface of the left arm just above the elbow. The wound healed quickly, and he had no symptoms referable to the ulnar nerve. In April 1941 he noticed the onset of weakness of the left hand and diminution of sensation in the area supplied by the ulnar nerve. In June 1943, on admission to another general hospital for a minor ailment, he was found to have almost complete paralysis of the left ulnar nerve. It was noted that all the muscles supplied by this nerve showed some response when tested with faradic and galvanic currents. On July 19 the ulnar nerve was explored above the elbow. At a point about 0.5 cm. from the epicondyle there was a firm nodule, 0.75 cm. in diameter, which involved the entire nerve trunk. This nodule was excised, together with 2 to 3 mm. of normal-appearing nerve tissue on either side of the mass. The severed ends of the completely interrupted nerve were then approximated and sutured. On microscopic examination the nodule showed interlacing bundles of nerve fibers, and a pathologic diagnosis of neuroma was made.

Examination at the time of admission to this hospital, on September 10, showed no abnormalities except those associated with the left ulnar nerve. There was pronounced atrophy of the interosseus and lumbricalis muscles but much less conspicuous wasting of the muscles of the hypothenar eminence. Sensation was completely absent over the distribution of the ulnar nerve. There was no voluntary motor activity in any of the muscles innervated by this nerve. The fourth and fifth fingers were continually in a position of firm flexion but could be straightened without difficulty on passive movement. Numerous spontaneous movements over the hypothenar eminence were easily visible. They appeared to be due to the synchronous activity of large groups of muscle fibers, having the appearance of the spontaneous fasciculations seen in degenerative disease of the lower motor neuron or after the administration of neostigmine. No such spontaneous movements were seen in any other region. During the three months in which the patient was observed each day there was a gradual and progressive decrease in the number of these spontaneous movements. However, a momentary increase in their rate could be effected by putting the muscles on a stretch. These abnormal movements had not been noted during his stay in the other hospital. The time of their onset could not be accurately determined, but they were present on admission to this general hospital.

Method.—To obtain an accurate picture of the activity, electrical recordings were made from abductor digiti quinti and other muscles of the hypothenar eminence, with the method of Harvey and Masland (1941).[3] In certain observations the potentials were led to the input of a condenser-coupled amplifier and recorded on a cathode ray oscillograph. In others, when continuous recording was necessary, a General Electric–Victor electrocardiograph was used. The motor nerve was stimulated by means of condenser discharges from gas discharge tube circuits, led through a specially shielded and balanced transformer.

Results.—The general pattern of spontaneous muscle activity could be recorded on an electrocardiograph (figure, *B*). The frequency of discharge was usually 8 to 10 per second, but at times it was lower. Simultaneously fine muscle movements could be observed through the skin. A more detailed picture of the individual discharges was seen in the records taken on a cathode ray oscillograph, as shown in *A* of the figure. The potentials in this record represent either the same

1. Tower, S. S.: The Reaction of Muscle to Denervation, Physiol. Rev. **19:**1, 1939.

2. Denny-Brown, D. E., and Pennybacker, J.: Fibrillation and Fasciculation in Voluntary Muscle, Brain **61:**311, 1938.

3. Harvey, A. M., and Masland, R. L.: Method for Study of Neuromuscular Transmission in Human Subjects, Bull. Johns Hopkins Hosp. **68:**81, 1941.

ELECTRIC CONVULSIVE THERAPY OF THE PSYCHONEUROSES

LOTHAR B. KALINOWSKY, M.D.; S. EUGENE BARRERA, M.D., AND
WILLIAM A. HORWITZ, M.D.

NEW YORK

The simplicity of electric convulsive therapy and its possible application to ambulatory patients seem to favor its indiscriminate use in treatment of all types of psychoneuroses. This possibility suggested a broader clinical investigation for the purpose of determining the actual value of this method for the neuroses. Another reason for such a therapeutic study was the expectation that a comparison of reactions in the neuroses and those in the major psychoses might contribute to a better understanding of

patients. Others [2] recommended it, and a compilation from the entire literature revealed a rather high incidence of improvement.[3]

Our material consists of 65 patients whose illness was severe enough to cause them to seek voluntary admission to the New York State Psychiatric Institute; many of them had been under observation for several months before being subjected to electric convulsive therapy. This period of observation permitted us not only to reduce the number of diagnostic errors but to exclude improvements due to change from the home environment and to the psychotherapeutic approach. Most of these patients had had psychotherapy prior to

Results of Electric Convulsion Therapy in Sixty-Five Psychoneurotic Patients

Type of Psychoneurosis	Total No. of Patients	Immediate Results			Later Development			Outcome Unknown
		Great Improvement	Slight Improvement	No Improvement	Great Improvement	Slight Improvement	No Improvement	
Obsessive-compulsive	16	5 (31.3%)	9 (56.2%)	2 (12.5%)	5 (35.7%)	4 (28.6%)	5 (35.7%)	2
Anxiety hysteria	15	2 (13.3%)	3 (20%)	10 (66.7%)	2 (14.3%)	1 (7.1%)	11 (78.6%)	1
Conversion hysteria	13	5 (38.5%)	2 (15.4%)	6 (46.1%)	2 (22.2%)	2 (22.2%)	5 (55.6%)	4
Mixed psychoneurosis	10	2 (20%)	4 (40%)	4 (40%)	1 (11.1%)	2 (22.2%)	6 (66.7%)	1
Reactive depression	11	10 (99.1%)	1 (0.9%)	..	7 (77.8%)	2 (22.2%)	..	2
Total	65	24 (36.9%)	19 (29.3%)	22 (33.8%)	17 (31%)	11 (20%)	27 (49%)	10

the effect of shock treatment in general. The difference between the effect of electric convulsive therapy and that of other organic methods applied in treatment of the neuroses promised to offer further points of interest.

Cerletti,[1] the originator of electric convulsion therapy was the first to try the method in a few cases of severe psychoneuroses, without more than transient results, which he attributed to autosuggestion. Many experienced investigators reported discouraging results, or even warned against the use of the method with neurotic

shock treatments and remained under the care of the psychotherapeutist during the convulsion therapy.

The accompanying table shows the results for patients with various types of psychoneuroses. A classification was chosen which, it was hoped, would facilitate control investigations, although it was realized that pure forms of psychoneuroses are rare and that a subtype can refer only to the predominant symptom presented by the individual patient. The table is offered as a basis for the discussion, but more importance is attributed to conclusions from our clinical observations.

The results with the various subtypes of the psychoneuroses will be discussed separately because they differ from each other in kind and in degree. The incidence of improvement in the whole group of 65 patients is of no interest because figures based on

1. Cerletti, U.: Electro-Shock, Riv. sper. di freniat. 64:209, 1940.

2. Moriarty, J. D., and Weil, A. A.: Combined Convulsive Therapy and Psychotherapy of the Neuroses, Arch. Neurol. & Psychiat. 50:685 (Dec.) 1943.

3. Impastato, D. J., and Almansi, R. J.: A Study of Over Two Thousand Cases of Electrofit-Treated Patients, New York State J. Med. 43:21, 1943.

the injection. No change could be detected in the frequency or size of the movements, or in the increased number of discharges following stretch.

It seemed of importance to determine the effect of neostigmine on these spontaneous twitchings, particularly as the possibility existed that acetylcholine might be concerned in the mechanism of their production. One milligram of neostigmine methylsulfate was injected into the brachial artery, and the venous return was occluded for one minute. The muscles innervated by the median and radial nerves became weak and within a short time were the seat of numerous spontaneous fasciculations. Voluntary strength gradually returned during the next ten to fifteen minutes, and the fasciculations persisted for thirty to forty minutes, as described in normal subjects by Harvey and Lilienthal.[5] In addition, there was a more general effect, with spontaneous twitchings in the tongue and the orbicularis muscle group. Continuous electrical recordings of the responses from the hypothenar group showed no detectable change in the type and degree of the spontaneous discharges during the thirty minutes following the injection.

COMMENT

From the observations which have been described it is clear that the spontaneous activity had its origin in denervated muscle. Furthermore, the action potentials produced demonstrated that the activity resulted from the synchronous discharge of groups of muscle fibers. Once such a discharge originated in a given area of the muscle it usually continued for many minutes with a definite rhythm. After stretch the activity was enhanced, and spontaneous impulses sometimes originated from several foci, each with its independent rhythm.

It is of interest that in each experiment the action potential spikes always passed the recording electrodes from the same direction, as determined by their polarity. This evidence is not conclusive but indicates that a comparatively small area possessed certain properties not found in other portions of the muscle and was able to give rise to these spontaneous discharges and to synchronize their activity.

Spontaneous synchronized discharges have been described during block in neuromuscular transmission and in denervated muscle of frogs in the presence of a deficiency of calcium.[6] It has also been demonstrated by one of us (S. W. K.)[7] that such discharges set up by a reduction of calcium ions during a period of neuromuscular block originate at the motor end plates.

There is evidence from other sources that activity can originate spontaneously at the end plate region. In the denervated diaphragm of the rat, fibrillary activity was shown by Hayes and Woolsey[8] to have its origin at the junctional regions. Forty to ninety days after motor denervation of frog muscle, bursts of impulses may arise at the end plates, particularly after stretch or mechanical stimulation, and continue for several minutes. Also, in cases of tetany fibrillary activity has been shown to originate at the end plates.[9]

Although it cannot be demonstrated conclusively, it is suggestive that the spontaneous activity in the present case may have originated in the region of the motor end plates. Such activity may be of more frequent occurrence than is realized, and with further observation more may be learned of its nature. It was not possible to determine whether this synchronous activity was coexistent with fibrillation in other muscle fibers, but it seems reasonable to assume that it had its origin in the same area of the muscle as this type of activity, which is uniformly present in denervated striated muscle. The rate of the spontaneous discharges in the present case was similar to that noted by other authors in fibrillating muscle fibers (Tower,[1] page 9). It is felt that the spontaneous activity in this case was nothing more than synchronized fibrillation.

SUMMARY

In an investigation of the spontaneous synchronized activity of groups of muscle fibers in muscles of the hypothenar eminence of a patient in whom the motor fibers of the ulnar nerve had been completely interrupted for four months, the following observations were made:

1. Electromyographic recordings showed muscle groups discharging at a frequency of 8 to 10 per second. The discharges tended to appear in constant rhythmic groups. The number of spontaneous movements could be greatly increased by stretching of the muscles.

2. Complete absence of innervation of the active muscles was demonstrated by various methods.

3. The origin and the synchronization of the activity may have occurred at the region of end plates in the denervated muscles.

4201 St. Paul Street, Baltimore.

5. Harvey, A. M., and Lilienthal, J. L.: Observations on Nature of Myasthenia Gravis: Intra-Arterial Injection of Acetylcholine, Prostigmine and Adrenaline, Bull. Johns Hopkins Hosp. **69**:566, 1941.

6. Kuffler, S. W.: Specific Excitability of the End-plate Region in Normal and Denervated Muscle, J. Neurophysiol. **6**:99, 1943.

7. Kuffler, S. W.: The Effect of Calcium on the Neuromuscular Junction, J. Neurophysiol. **7**:17, 1944.

8. Hayes, G. J., and Woolsey, C. N.: The Unit of Fibrillary Activity and the Site of Origin of Fibrillary Contractions in Denervated Striated Muscle, Federation Proc. **1**:38, 1942.

9. Kuffler, S. W.: Excitability Changes at the Nerve-Muscle Junction During Tetany, to be published.

dispensable condition for the production of remissions with electric convulsive therapy.

Mixed Psychoneuroses.—Although most psychoneuroses are of "mixed" type, only a small group of patients had to be classified under this head because no well defined symptoms predominated. Nothing need be added to the observations made on the patients in the other groups. We may mention here the experiences of other authors with certain ill defined forms of neurosis. Myerson [4] noted good results in cases of a chronic neurosis which he described as an "anhedonic state." Favorable results were likewise reported by Kennedy and Wiesel [5] in patients with a so-called manic-depressive equivalent, persons with episodes of somatic complaints and only moderate depression.

COMMENT

The subjective reaction of the patient to the experience of the treatment should be commented on. What some patients describe as "feeling at ease as never before" is complained of by others as "losing control of myself." Complaints are manifold. One patient said that he could not see as clearly as before the treatment, but he added, "It might not be so much my eyesight as my mind." After a greater number of treatments the patients become indifferent. One who had relapsed commented: "During the treatment I felt just swell; I was in a fog, and therefore nothing bothered me." The opinion has been expressed that neurotic patients show more severe memory defects than psychotic patients. Closer observation reveals that it is only the reaction to this impairment which is felt more intensely by neurotic patients. One patient refused treatment because he was afraid that owing to his impairment of memory the physicians would make him think what they wished and that he would lose control of the situation. Others were afraid of becoming insane. At a time when tests already showed the disappearance of all traces of memory defect, the neurotic patient might still hold the treatment responsible for any difficulty he might have in remembering things.

Before we proceed to a final evaluation of our results with this treatment, attempts to treat psychoneurotic patients by other organic methods should be discussed. Insulin shock therapy has been used little with neurotic patients. A favorable influence, especially with patients suffering from anxiety neuroses, has frequently been reported. Since metrazol, like the electric current, is a convulsive agent, comparison of the results with these two agents is of greater interest. Shapiro and Freeman [6] reported good results with metrazol; in their experience improvement usually did not appear before at least a slight confusional state was reached. They took exception to the theory that fear is the therapeutic agent. Other authors have stressed the importance of the anxiety between the time of injection and the appearance of a convulsion for the successful treatment of psychogenic symptoms. This might explain the apparent superiority of metrazol over electric convulsive therapy in certain cases of acute neurotic reactions, e. g., war neuroses.

The best results of an organic treatment of neurotic patients were described by Freeman and Watts,[7] with frontal lobotomy. This operation and electric convulsive therapy have in common the organic interference with cerebral functions, which, however, is transitory in the case of convulsive treatment, but permanent, and therefore of more lasting therapeutic effect, in the case of frontal lobotomy. Psychosurgery and electric convulsive therapy produce "blanching of the emotional coloring connected with obsessive ideas," relief of tension and certain unpleasant organic side effects, such as unrestrained behavior and impaired judgment. But both the side effects and the improvement are of short duration with electric convulsive therapy. The superiority of the operative procedure is illustrated by 1 of our cases.

F. A., a man aged 32, since 1939 had suffered from the obsession of not being able to breathe. He had to watch his respiration every moment and was unable to concentrate on anything else. In 1942 he applied for voluntary admission to the Pilgrim State Hospital, where he received twenty electric convulsive treatments. After ten treatments the obsessive idea had lost its importance for him; after sixteen treatments it had disappeared completely, but this was only part of a Korsakoff-like syndrome. Ten days after the last treatment the obsession returned, and six weeks after the end of therapy the patient suffered as much as before. Ten months later a frontal lobotomy was performed by Dr. T. J. Putnam, with full success. The patient has now been under the observation of the New York State Psychiatric Institute for five months since the operation. He lost his obsessions

4. Myerson, A.: Further Experience with Electric Shock Therapy in Mental Diseases, New England J. Med. **227:**403, 1942.

5. Kennedy, F., and Wiesel, B.: A Report on the Results of Electric Shock Treatment on Mental and Emotional Symptoms, New York State J. Med. **42:** 1663, 1942.

6. Shapiro, H. D., and Freeman, W.: Shock Therapy (Insulin and Metrazol) in the Neuroses, M. Ann. District of Columbia **8:**65, 1939.

7. Freeman, W., and Watts, J. W.: Radical Treatment of Psychoses and Neuroses, Dis. Nerv. System **3:**6, 1942.

mixed material depend entirely on the ratio between the number of patients with a favorable and the number with an unfavorable prognosis.

RESULTS

Obsessive-Compulsive Neuroses. — The reaction of patients with this condition showed certain features in common: The sudden, dramatic improvement after three or four treatments, so common in psychotic patients, was not observed. However, there was frequently a gradual change after six, eight or more convulsions. At this point, the patient still retained his obsessive-compulsive symptoms, but his emotional response to them was lessened. They did not bother him so much, and he felt more at ease. When therapy was continued for twenty sessions, the patient who became deeply confused sometimes lost all recollection of his compulsions or obsessions. But closer observation revealed that this loss was only part of a farther-reaching amnestic syndrome, which was not limited to forgetting of his symptoms. It soon became obvious that the "recovery" from his obsessions and compulsions was a sham one. Discontinuation of treatment in most instances led to reappearance of the obsessive-compulsive symptoms in one or two weeks, that is, when the mental symptoms of organic origin had disappeared.

A small number of patients benefited more lastingly from the treatment. Even though the symptoms returned, they were accepted by the patient as something of less importance which did not interfere greatly with his activities. It is at this time that psychotherapy has its best chances. The patient, who is far more accessible, may be helped to become interested in his personal and professional life and enabled to take up his activities outside the hospital. Such occasional results justify an attempt to treat certain patients with a severe obsessive-compulsive neurosis which could not be influenced otherwise. A few surprising results in this group suggested a possible relation of the disorder to the psychoses.

Anxiety Hysteria.—Anxiety is probably the most frequent symptom encountered in neurotic patients, and it is also the symptom least amenable to electric convulsive therapy. Some patients may become temporarily relaxed, less tense and thus more accessible to psychotherapy. As a whole, however, patients with anxiety hysteria benefited least from the treatment. The condition of most of the patients remained unimproved during the entire course of treatment; some became worse or were frightened by the treatment. The few who improved slightly under treatment had a relapse after a short time.

Conversion Hysteria.—The results of treatment of conversion hysteria were almost as unsatisfactory. The hysterical character cannot be influenced and is a hazardous factor in the patient's reaction to the treatment. Hysterical symptoms may occasionally be effected, as with every method, but new symptoms may be brought out by the treatment. Improvement, such as that of a patient with hysterical paralysis, was strikingly reminiscent of the suggestive influence of faradic and other nonconvulsive electric treatments, as used formerly in the management of gross manifestations of hysteria. When we state this, we wish to make it clear that by no means do we agree with those who explain all improvement occurring during shock therapy by suggestion or by the terrifying effect reminiscent of methods applied in treatment of the psychoses centuries ago.

It should be noted that it is particularly the patients with conversion hysteria who complain of being made worse. Muscular pain, frequent in all patients receiving electric convulsive treatment, is often attributed to the heart or to other organs. Some patients elaborated on the experience of dizziness or other sensations during the period of awakening or were terror stricken by the amnesia. One patient reacted with a Ganser syndrome of short duration after only two treatments. The patients who showed improvement were chiefly those who, impressed by recovery in others, had requested shock therapy or those in whom the conversion syndrome was accompanied by a strong depressive element.

Psychoneurotic Depressions.—The best results were observed in treatment of the so-called psychoneurotic depressions. Like manic-depressive and involutional depressions, the depressions of neurotic patients had a remission after approximately four treatments, although the neurotic setup remained unchanged. It depended on the seriousness of the patient's neurotic attitude whether or not his readjustment succeeded. Some of the patients received a strong stimulus from the euphoric reaction which often followed the treatment. Failure is illustrated by the case of a physician who, suffering from a psychoneurosis of long standing, had gone into a depression. When cured of his depression, his energy returned but fizzled out in unproductive activities, and his neurotic attitude prevented him from returning to work. However, the majority in this group benefited from the treatment. The shock treatments should be followed by psychotherapy, which with other types of depressions was found to be a desirable, but not in-

whom treatment is hazardous because they may react to unpleasant sensations during the treatment with the development of new symptoms. Only when such symptoms may substitute for a depressive episode or when psychotherapy has failed might electric convulsive therapy be tried. Extreme caution should be applied in the selection of patients, and the availability of a simple mechanical method should not prevent the psychiatrist from using a psychologic approach to the patient's psychologic problems.

The situation is different in the case of patients with a severe obsessive-compulsive neurosis of long standing. If such patients have lost their social usefulness and their joy of living and if adequate psychotherapy has failed, or cannot be afforded, an attempt with electric convulsive therapy is justified. A point in favor of the use of electric convulsion therapy is the possibility that neurotic symptoms are the first clinical expression of a psychosis. Occasional improvement in cases of obsessive-compulsive neuroses stimulates speculation regarding the relation of this condition to schizophrenia.

Psychoneurotic depressions should be treated in any case in order to clear the depression, even if the patient may remain neurotic. Many cases of an apparently reactive depression are actually cases of a manic-depressive psychosis, for which convulsive therapy is the treatment of choice. It is equally justifiable to treat the ill defined neuroses of episodic character in which physical complaints and general listlessness are clinical expressions of an underlying depression.

The optimal number of treatments, satisfactorily determined in our experience for the various major psychoses, cannot easily be stated for the neuroses. In patients for whom treatment is intended mainly to relieve tension and to overcome resistance to psychotherapy, a series of a few treatments, with longer intervals and avoidance of confusional states, is preferable. For depressive syndromes the optimum will be six to eight treatments, as given for other depressions. For obsessive-compulsive neuroses twenty treatments, considered as a minimum in treatment of schizophrenia,[12] are given in order to achieve at least temporary disappearance of obsessive thoughts and compulsions.

Our experience does not permit as clear a statement for or against electric convulsion therapy for the psychoneuroses as can be made regarding its value for the manic-depressive and involutional psychoses, as well as for acute schizo-

phrenia. In general, the final results with neurotic patients are unsatisfactory. It may be stated, however, that careful selection of patients and well planned application in combination with psychotherapy lead to fair results in a limited number of patients. The improvement does not resemble, either in type or in degree, that obtainable with a proper application of electric convulsive therapy with certain types of psychoses.

722 West One Hundred and Sixty-Eighth Street.

ABSTRACT OF DISCUSSION

Dr. A. E. Bennett, Omaha: The authors obtained their best results with psychoneurotic depressions. Patients responded after four treatments, but the authors recommend adjunctive psychotherapy. They noted improvement after the fourth treatment in depressions similar to the affective disorders of the psychoses. The only other effect of treatment was organic forgetfulness, similar to narcosis induced by barbiturates. They express the belief that neurotic persons respond poorly to convulsive shock therapy but that psychologic treatment is helpful; yet psychologic treatment fails in therapy of the psychoses. They miss the point, since good results depend on the degree of affective involvement associated with the psychoneurosis or the psychosis. After a certain degree of affective deterioration occurs, psychotherapy is not effective, and a schizophrenic process may be established. Shock therapy is likewise ineffective unless a distinct organic syndrome is superimposed. The authors conclude that the poor results do not exclude the use of electric shock therapy in well selected cases, but they discourage its employment for the treatment of anxiety neurosis and hysteria. They state that "only when such symptoms may substitute for a depressive episode or when psychotherapy has failed should electric convulsive therapy be tried."

The crux of this discussion is whether one can separate the psychoses from the neuroses; many neurotic symptoms are the first expression of a psychosis. Obsessive states often develop into schizophrenia and anxiety states into depressions. Psychoneurotic depressions respond in the same way as reactive, manic-depressive and involutional depressive states; it is a question of the degree of involvement by the affective depression.

In their conclusions the authors are unable to give a clearcut statement for or against convulsive therapy for the psychoneuroses, as they were able to do for manic-depressive and involutional states. I disagree with their contention that the method is effective with acute schizophrenia, but in selected cases good results are obtained.

The authors miss the point which I emphasized in my original paper [13] concerning the value of convulsive shock therapy, namely, that convulsive therapy is a near specific for affective disorders and of little value in schizophrenia. The improvement is determined by the degree of affective reaction of the patient, whether the reaction is schizophrenic or psychoneurotic; this suggests that only two types need be considered from the standpoint of the response to convulsive shock

12. Kalinowsky, L. B.: Electric Convulsive Therapy, with Emphasis on Importance of Adequate Treatment, Arch. Neurol. & Psychiat. **50**:652 (Dec.) 1943.

13. Bennett, A. E.: Convulsive (Pentamethylentetrazol) Shock Therapy in Depressive Psychoses, Am. J. M. Sc. **196**:420 (Dec.) 1938.

immediately after the operation, although he remembers them well; however, he offers pronounced character changes since the operation.

In spite of the superiority of the results of the operative procedure in treatment of obsessive-compulsive neurosis, the small risk of electric convulsive therapy and the occasional good results make advisable a trial of the latter treatment prior to the operation.

One of the purposes of this study was a comparison of the type of response to electric convulsive therapy in neurotic and in psychotic patients. There is one striking difference: Psychotic syndromes which respond favorably to convulsive treatment are broken up suddenly after the third or fourth convulsion, i. e., at a time when the sensorial blurring is still negligible. This characteristic response in psychotic patients was not seen in any of the neurotic patients in our series except those with depressions. Most neurotic patients who improved did so gradually, and only with the appearance of such organic mental symptoms as greater emotional responsiveness, accessibility and suggestibility. The disappearance of neurotic symptoms is rarely as complete as that of certain psychotic syndromes. In some cases, however, the patient forgets his symptoms for a time, shows less emotional response to them and thus may be helped to overcome his illness in a way similar to that observed with the use of sodium amytal. Another element not seen in psychotic persons is the factor of suggestion, as exemplified by patients who were anxious to have the treatment and who improved after one application.

With most of our patients psychotherapy prior to electric convulsive therapy had failed but was used during, as well as after, the shock treatment. In favorable cases the two methods of treatment should be given equal credit because of the better psychotherapeutic accessibility after electric convulsive therapy.[8] This experience is in contrast to that with psychotic patients, with whom excellent results can be obtained without psychotherapy.

The poor response of neurotic patients to electric convulsive therapy and the good results with psychotic patients are of great interest. Conversely, psychologic methods of suggestion and persuasion are helpful in treatment of the neuroses but fail largely with the psychoses. If the effect of electric convulsive therapy were explainable on psychologic grounds, neurotic patients should respond better than psychotic patients. The reverse is true, and even a psychoneurotic admixture in cases of the major psychoses largely diminishes the chance for a remission under shock therapy. It may be added that subconvulsion responses in electric shock therapy, representing in some respects the same psychologic situation for the patient as convulsive responses, are ineffective in psychotic patients,[9] but may lead to improvement in neurotic patients. The difference between the effect on neurotic patients and that on psychotic patients will be of interest for future studies on the effective agent in shock therapy.

CONCLUSIONS

The question of the advisability of electric convulsive therapy of a psychoneurosis is far more difficult than the advisability of such treatment for the major psychoses. For the affective disorders and for schizophrenia the shock therapies are the only methods in general use, and the results are gratifying in a considerable number of patients. For treatment of the neuroses psychologic methods are available, and electric convulsive therapy would be indicated only if the results were superior. Statistical reports on the results of psychotherapy with the neuroses, regardless of the form used, seem to vary within narrow limits, as has been observed only recently with war neuroses.[10] In most statistics on peacetime neuroses the percentage of patients showing improvement ranges between 60 and 70 per cent when persons showing great improvement and those showing slight improvement are considered together.[11] Our figures for electric convulsion therapy reach these values only for a few types of neurotic patients.

On the other hand, the results do not preclude the use of electric convulsive therapy in well selected cases. The actual dangers of this method are so few that one is justified in discussing indications purely from the point of view of expected results. The following recommendations are made on the basis of clinical experience with the series of 65 neurotic patients presented in this paper.

Patients with anxiety neurosis should be excluded from treatment because they have the poorest chance of improvement. The same holds good for patients with conversion hysteria, for

8. Selinsky, H.: The Selective Use of Electroshock Therapy as an Adjuvant to Psychotherapy, Bull. New York Acad. Med. **19**:245, 1943.

9. Kalinowsky, L. B.; Barrera, S. E., and Horwitz, W. A.: The "Petit Mal" Response in Electric Shock Therapy, Am. J. Psychiat. **98**:5, 1942.

10. Slater, E.: The Neurotic Constitution, J. Neurol. & Psychiat. **6**:1, 1943.

11. Curran, D.: The Problem of Assessing Psychiatric Treatment, Lancet **2**:1005, 1937.

regimen during the time of recovery the anxiety could often be overcome to a greater or less extent in the period to follow.

It is fortunate that there is so much disagreement with regard to electric shock therapy of the neuroses, since only by discussion and further experiments can this method of treatment be properly evaluated. For that reason Dr. Kalinowsky's paper is provocative.

DR. LOTHAR B. KALINOWSKY, New York: The difference in the interpretation of Dr. Bennett's results and our own is explained by a difference in concept regarding the line of demarcation between the neuroses and the psychoses. Anxiety is a term which my colleagues and I would not apply to the emotional state of a patient with an agitated depression. Of course, the excellent response of such patients to convulsion therapy is recognized, since Dr. Bennett demonstrated it in the work to which he referred. The complete difference in the response of patients with agitated depression and that of patients with anxiety neurosis is another argument in support of the opinion that the neuroses and the psychoses have a different basis. I do not think a typical anxiety neurosis ever passes over into the psychotic picture of an agitated depression.

I cannot agree with what has been said about electric convulsive therapy in cases of schizophrenia in which good results can be achieved with adequate treatment; that is, when twenty and more treatments are given, even though the patient becomes temporarily free from symptoms after as few as four or five. It is interesting to speculate whether the obsessive-compulsive neuroses which show a good response to electric convulsive therapy are more closely related to schizophrenia. The relation between obsessive-compulsive neurosis and schizophrenia has been frequently discussed. One might look here for the answer to the problem of why a small percentage of patients with obsessive-compulsive neurosis, contrary to the reactions of most other neurotic patients, respond to a method originally advised for the treatment of schizophrenia.

We get the best results from shock therapy in patients with dramatic symptoms. Patients with neurotic symptoms superimposed on a phychosis and patients with borderline conditions in which the personality is well preserved show the poorest response to treatment. I have no explanation to offer for this, but I think it is one of many experiences in shock therapy which are of the greatest interest to the basic concepts of psychiatry and which should be studied without bias from previous psychiatric concepts.

therapy: (1) schizophrenic-like states, including obsessive-compulsive, paranoid and certain hysteriod states, which carry a poor prognosis, and (2) affective disorders, including all types of pure depression, manic excitement, involutional depression, psychoneurotic depression, depression with obsessive features and certain catatonic states with depressive features, all of which respond to convulsive shock therapy induced either by drugs or by the electric current.

DR. LLOYD H. ZIEGLER, Wauwatosa, Wis.: The meaning of the diagnosis psychoneurosis varies somewhat from one clinic to another. Sometimes it is applied to the early phases of a disorder which changes so that later a different diagnosis must be made. So-called psychoneurotic manifestations are not infrequent in the course of a substantial psychosis. Neurotic patients may become psychotic. A mild depression is often diagnosed as a neurasthenic (or anhedonic) state. The neuroses encountered in state hospitals are somewhat more tenacious than those met with in office practice. It is apparent that when human nature goes askew, it may not do so in the form of a simple, clearcut, unmixed syndrome. For several years I have been aware of the instability, and often the lack of meaning, of the terminology of diagnostic psychiatry.

If the emotions are meager, undeveloped, poorly used or unwisely conditioned over a long period, electric shock therapy will not give the patient new ones. Hallucinations have been known to disappear after electric shock therapy, but this does not occur regularly. False thinking may right itself after electric shock. An extensive therapeutic survey is needed to demonstrate what effect electric shock therapy (or any other method of treatment, for that matter) may have on numerous disabling symptoms and signs in various combinations and of various durations, regardless of the one or two word psychiatric diagnosis proposed. In this the authors have already made a start.

Compulsive-obsessive neuroses appear to be of two types: One has an insidious onset early in life and is usually tenacious. In my experience, electric shock therapy has not been helpful with this form. Prefrontal lobotomy has benefited some patients. The other type of the neurosis occurs in the form of attacks with fairly abrupt onset and is often associated with considerable depression. This neurosis responds well to electric shock treatment.

Anxiety is a symptom which permeates to the very core of a person, usually disabling him severely. It is a primitive, stubborn and tenacious form of defensiveness. The anxious patient's behavior may be dramatic, and he appeals to the deepest sympathies and concern of persons about him. When anxiety is associated with depression, I have seen it respond to electric shock treatments. Anxiety alone, or conversion symptoms alone, which may be the chief overt defenses of an unstable person, are not responsive to electric shock therapy. There are other methods of dealing with such symptoms somewhat more effectively.

On the whole, electric shock is purely specific in breaking up depressed or elated states, or their clinical equivalents, which come on largely in circumscribed attacks. In so far as these states are complicated by symptoms which are usually called neurotic, the results of electric shock may be attenuated considerably.

Stress in wartime may be so great that any one will break under it sooner or later. Some of these "breaks" appear as syndromes resembling the so-called neuroses. The release of the stress of war, unless it has persisted too long, or unless the person is especially predisposed by nature, often suffices for recovery. This merely shows that predisposition to disorders of human nature exist in every one, but to a variable degree. Some persons are almost immune, and these are sought as the most desirable for active military duty. Rarely does civilian life approximate the quality and degree of the acute and accumulative strain imposed by war. This suggests that the subtly concealed chronic stresses and strains of the neurotic person in civilian life should be investigated and relieved, if possible. I fear that this may ultimately require more than what is called psychotherapy. From what is known of electric shock, it does not benefit more than a few types of patients, as previously mentioned. In this the neurotic and the schizophrenic patients appear to have much in common.

DR. V. E. GONDA, Chicago: There is serious disagreement as to what constitutes one or another type of psychosis or psychoneurosis. Dr. Bennett and Dr. Ziegler have presented diverse opinions. The time seems to have come for a specific agreement in the matter of diagnosis. From the statements of the various speakers, one must conclude that there is practically no known psychosis or psychoneurosis, or any of the subgroups, that could or could not be cured by electric shock therapy. One is indeed lost in the maze of these contradictions.

It is generally accepted that the milder types of psychoneuroses do not respond as well to electric convulsive therapy as do the more serious forms and that the psychoses react with good results only when the treatments are adequate in number and are sufficiently supported by psychotherapy. Whenever, in association with a long-standing psychoneurosis, there develops a depressive state, whether or not it is severe, the patient should be given the benefit of convulsive therapy, if for no other reason than that excellent results are obtained with this method in the treatment of the depressive state.

If it were proved that electric convulsive treatment influences the course of the psychosis more favorably than the course of the psychoneurosis, it might be used in doubtful cases as a differential diagnostic procedure.

DR. TOM B. THROCKMORTON, Des Moines, Iowa: This discussion brings out the conclusion to which I have come, namely, that in patients with true schizophrenia and in persons with various well grounded and fixed fears there is little to be hoped for in improvement or cure from the use of induced convulsive seizures.

I only wish there were some means by which these unfortunate persons could be offered something which would enable them to be rid of their delusions or of their fears, but I am afraid induced convulsive seizures have little promise.

DR. WALTER B. FREEMAN, Washington, D. C.: My first conclusions with respect to the treatment of the psychoneuroses with convulsive shock therapy have been borne out only partially. In other words, the obsessive-compulsive reactions have tended to undergo relapse. On the other hand, my experience in cases of conversion hysteria has been good, even when there was a distinct compensation element.

In treatment of the anxiety states I look on electric shock as a means of overcoming the resistance of the patient to a program of activity designed to allay his symptoms of anxiety. In a number of cases of profound anxiety reactions my associates and I have found that after the electric shock treatment, which was given intensively (perhaps six convulsive attacks in eight days), the patients would walk 5 or 10 miles (0.8 or 1.6 kilometers) a day, and that by observation of such a

Weed[7] had previously pointed out that the morphologic character of these mesothelial lining cells varied with their function. Essick confirmed this observation when he noted that in response to laked blood the normally flat lining cells passed through stages of becoming rounded, of enlarging, of assuming active phagocytosis while still attached to the trabeculae and, finally, of breaking off as free phagocytes in the cerebrospinal fluid. Essick's work on cats has recently been confirmed by Finlayson and Penfield,[8] who used human subdural hematoma fluid as the irritant. In the same year Ayer[9] arrived at essentially the same conclusions, using other experimental animals. Still further confirmation was offered by Woollard,[10] in 1924.

That blood can cause not only a transient meningitic response but permanent fibrosis and obstruction to the flow of cerebrospinal fluid was shown in pups and adult dogs by Bagley,[11] in 1927. He observed that the intrathecal injection of blood caused symptoms varying in degree of intensity up to severe convulsions. Studies showed an increase of fibrous tissue in the meninges after several weeks and, in many of the pups, moderate ventricular dilatation.

In an excellent series of papers, Bagley[12] bridged the gap between experimental and clinical observations by means of a study of the meninges in cases representing various types of cerebral and subarachnoid hemorrhage. He observed a transient meningeal reaction with marked phagocytosis and, at a later stage, fibrotic thickening of the meninges, which was most pronounced at the base of the brain and in the sulci of the cerebral hemispheres, where the pia was matted together by fibrous tissue. In 1 of his cases, that of an infant 18 days of age, he attributed the presence of internal hydrocephalus to fibrosis and obstruction in the region of the foramens of Magendie and Luschka. In another case of fibrosis of the leptomeninges following subarachnoid hemorrhage a communicating type of hydrocephalus suggested interference with absorption of the cerebrospinal fluid along the longitudinal sinus. Bagley concluded that patients with subarachnoid hemorrhage should be treated by drainage of the irritant fluid. Mild hemorrhage in adults may be followed by complete recovery without drainage, but hemorrhage in infants, if untreated, frequently leads to hydrocephalus, muscular rigidity and epilepsy.

In many of Bagley's cases the condition either developed after operation or was the result of trauma to the head. The same is true of the human material studied by Finlayson and Penfield, since their interest lay primarily in a clinicopathologic investigation of the effect of blood in the subarachnoid space following intracranial surgical procedures. Accordingly, in the only two large series of cases reported in which the meningeal reaction to blood was studied in man, the factors of (1) possible infection, either postoperative or secondary to fracture of the skull, and (2) exposure of the meninges to the atmosphere introduced variables which might theoretically influence the meningeal response.

A review of the many reports of cases in the literature dealing with spontaneous subarachnoid hemorrhage proved disappointing with regard to mention of meningeal changes. Necropsy reports are confined primarily to a description of the source of the hemorrhage or of the type of aneurysm, if one was present. Reports by Herndon,[13] Strauss, Globus and Ginsburg[14] and Turner[15] contain the mention of a meningeal reaction, with the presence of polymorphonuclear leukocytes, lymphocytes and, later, fibrosis. In none of these cases were there symptoms or evidence at necropsy of interference with the flow or absorption of cerebrospinal fluid. Smith[16] and Merwarth and Freiman,[17] however, each reported a case of hydrocephalus following subarachnoid hemorrhage in a child. In each case

7. Weed, L. H.: An Anatomical Consideration of the Cerebro-Spinal Fluid, Anat. Rec. **12**:461-496 (May) 1917.

8. Finlayson, A. I., and Penfield, W.: Acute Postoperative Aseptic Leptomeningitis: Review of Cases and Discussion of Pathogenesis, Arch. Neurol. & Psychiat. **46**:250-276 (Aug.) 1941.

9. Ayer, J. B.: A Pathological Study of Experimental Meningitis from Subarachnoid Inoculation, Monograph 12, Rockefeller Institute for Medical Research, 1920, pp. 26-44.

10. Woollard, H. H.: Vital Staining of the Leptomeninges, J. Anat. **58**:89-100 (Jan.) 1924.

11. Bagley, C., Jr.: Blood in the Cerebrospinal Fluid: Resultant Functional and Organic Alterations in the Central Nervous System, Tr. South S. A. **40**:369-392 (Dec.) 1927; Arch. Surg. **17**:18-81 (July) 1928.

12. Bagley, C., Jr.: Spontaneous Cerebral Hemorrhage: Discussion of Four Types, with Surgical Considerations, Tr. South S. A. **44**:448-484 (Dec.) 1931; Arch. Neurol. & Psychiat. **27**:1133-1174 (May) 1932; footnote 11.

13. Herndon, R. F.: Spontaneous Subarachnoid Hemorrhage, Illinois M. J. **75**:73-80 (Jan.) 1939.

14. Strauss, I.; Globus, J. H., and Ginsburg, S. W.: Spontaneous Subarachnoid Hemorrhage: Its Relation to Aneurysms of Cerebral Blood Vessels, Arch. Neurol. & Psychiat. **27**:1080-1132 (May) 1932.

15. Turner, C. C.: Spontaneous Subarachnoid Hemorrhage, South. M. J. **34**:949-954 (Sept.) 1941.

16. Smith, W. A.: Spontaneous Subarachnoid Hemorrhage, South. M. J. **23**:494-500 (June) 1930.

17. Merwarth, H. R., and Freiman, I. S.: Hydrocephalus Following Subarachnoid Hemorrhage: Report of Case with Pathologic Study, Brooklyn Hosp. J. **1**:149-157 (July) 1939.

REACTION OF THE MENINGES TO BLOOD

ERNEST M. HAMMES Jr., M.D.

Fellow in Neurology, Mayo Foundation

ROCHESTER, MINN.

In the relatively short space of forty years, subarachnoid hemorrhage has passed out of the category of a purely pathologic diagnosis to become a clinical entity capable of being recognized with almost absolute certainty during life. Gull,[1] in speaking of this condition in 1859, stated that "we have at best no symptoms upon which to ground more than a probable diagnosis." However, the introduction by Quincke,[2] in 1891, of lumbar puncture and the establishment by Froin,[3] in 1904, of the criteria necessary to distinguish the cerebrospinal fluid in cases of spontaneous subarachnoid bleeding from that in cases of traumatic lumbar puncture made possible the antemortem diagnosis in a large percentage of cases. Interest in subarachnoid hemorrhage lagged another twenty years, however, until the first careful clinicopathologic study was presented by Symonds,[4] in 1924.

The awakened interest in subarachnoid hemorrhage inevitably has brought forth many problems concerning the cause and therapy of this condition. The increase in trauma of all types, including traumatic subarachnoid hemorrhage, as a result of the present war serves as a further stimulus to investigation of the numerous phases of the subject of intracranial bleeding in general.

Outstanding among the unsolved problems relating to subarachnoid hemorrhage is the question of the harmful or beneficial effects of spinal drainage in the management of patients suffering from this condition. Opinions in the literature are about equally divided on this point. Broadly speaking, observers who advocate the procedure as a therapeutic aid feel that the removal of bloody spinal fluid at frequent intervals combats the danger of increased intracranial pressure and decreases a potential source of irritation to the meninges. Observers who believe that lumbar puncture is unwise, except possibly as a means of confirming the diagnosis, argue that nature will absorb the blood without interference and that the reduction of cerebrospinal fluid pressure can be dangerous only by removal of a protective barrier which, by a tamponade effect, is preventing further bleeding from the already ruptured vessel.

A factor which must be considered in evaluating the problem of therapeutic lumbar puncture in cases of subarachnoid hemorrhage is the reaction of the meninges to blood, for if it were found that blood is well tolerated by the pia-arachnoid one of the major arguments in favor of spinal drainage would be nullified. Accordingly, it was the purpose of this study to determine whether or not autogenous blood, in the absence of infection, is capable of causing a reaction in the meninges and, if so, to find out the nature of that reaction.

The earliest published suggestion of a meningeal reaction following spontaneous subarachnoid hemorrhage is to be found in a case report by Bramwell,[5] in 1886, in which he described "a localized collection of corpuscles, apparently indicative of a localized periarteritis" around the ruptured aneurysm of a patient who had died of spontaneous subarachnoid hemorrhage. From the experimental standpoint, Essick,[6] in 1920, investigated the effect of laked blood on the meninges of cats. He observed that full-blown sterile meningitis developed within six hours and was gradually replaced in forty-eight hours by large mononuclear phagocytes, which he observed forming from the arachnoid lining cells.

Abridgment of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Neurology and Psychiatry.

1. Gull, W.: Cases of Aneurism of the Cerebral Vessels, Guy's Hosp. Rep. 5:281-304, 1859.

2. Quincke, cited by Levinson, A.: Cerebrospinal Fluid in Health and in Disease, St. Louis, C. V. Mosby Company, 1919, chap. 1, pp. 17-30.

3. Froin, G.: Les hémorragies sous-arachnoïdiennes et le mécanisme de l'hématolyse en général, Paris, G. Steinheil, 1904.

4. Symonds, C. P.: Spontaneous Subarachnoid Haemorrhage, Quart. J. Med. 18:93-122 (Oct.) 1924.

5. Bramwell, B.: Clinical and Pathological Memoranda, Edinburgh M. J. 32:1-11 (July) 1886.

6. Essick, C. R.: Formation of Macrophages by the Cells Lining the Subarachnoid Cavity in Response to the Stimulus of Particulate Matter, Contribution 272, Carnegie Institution of Washington, 1920, pp. 377-388.

The incidence of intracerebral hemorrhage in nearly half the cases is surprisingly high and merits further discussion. As was to be expected, the majority of the intracerebral hemorrhages occurred in the frontal or the temporal lobe, usually at the base. None was observed in the occipital lobe, the cerebellum or the brain stem.

MENINGEAL RESPONSE TO SUBARACHNOID BLEEDING

Gross examination of the meninges in cases in which the patients had died at various intervals after rupture of an intracranial aneurysm failed to reveal any consistent change other than variable amounts of blood in different stages of degeneration. In all cases in which the patient had survived the first few days of the illness, only to die later of subarachnoid hemorrhage, there was clinical or postmortem evidence, or evidence in the cerebrospinal fluid, of fresh bleeding on one or more occasions. In some instances such an episode had occurred as many as four times within a month before the patient died. These attacks of bleeding cannot be considered evidence of recurrent subarachnoid hemorrhage in the usual meaning of the term, since they invariably represented fresh bleeding from the same site before the ruptured artery had had a chance to heal. This point is stressed because it constitutes an unavoidable limitation to determination of the duration of any phase of the meningeal reaction following exposure to blood. The ideal situation, of course, would be a series of cases in each of which there had been a single massive hemorrhage, with no further bleeding until death. If, however, the meninges are exposed to a new hemorrhage at several, irregular intervals prior to death, each hemorrhage will exert an effect on the reaction and will modify the postmortem appearance accordingly. This limitation was constantly kept in mind in the attempt to evaluate the changes now to be described.

Sudden Death.—In 9 of the 53 cases death had taken place within ten minutes of onset of the first symptom, and the majority of the patients were totally unaware of impending catastrophe at the time they became ill. Spontaneous subarachnoid hemorrhage is probably the commonest intracranial cause of nontraumatic sudden death of apparently healthy persons. Martland [21] obtained evidence of this condition in 2 per cent of 2,500 necropsies performed on the bodies of persons who had died suddenly without a history or external evidence of violence. The opinion expressed by Ayer [22] that death may follow spontaneous subarachnoid hemorrhage in as short a time as thirty-five minutes, but is never instantaneous, is at variance with the frequency of sudden death in the present series.

Microscopically, the subarachnoid space was observed to be filled with fresh blood cells, which passed into the sulci but were sharply delimited by the pia and arachnoid. Blood cells were rarely seen in the Virchow-Robin perivascular spaces; it was not common to see blood filling a sulcus but failing to enter the mouth of a Virchow-Robin space which connected with that sulcus. The reason for failure of the blood to penetrate these perivascular spaces is probably to be found in their small diameter and in the fact that the normal direction of flow along them is centrifugal, toward the subarachnoid space, as was shown by Weed [28] and Hassin.[24] As was to be expected, the blood was most prominent around the base of the brain, in the large cisterns, since the site of hemorrhage was in this region. However, considerable blood also was diffused over the convexity of the cerebral hemispheres and down the spinal cord to the theca. No reaction was seen in the meninges.

Death in One to Four Hours.—The earliest evidence of meningeal reaction was seen in cases in which the patients had survived two hours. The evidence consisted of small collections of polymorphonuclear leukocytes around the blood vessels of the pia. The microscopic appearance of the meninges was otherwise identical with that seen in examination of the tissues in the cases in which sudden death had occurred.

Death in Four to Sixteen Hours.—Patients who had survived four hours had sustained a more intense polymorphonuclear reaction, which had tended to become diffuse throughout the pia-arachnoid (fig. 1). No difference was noted between the reaction at the bottoms of the sulci and that over the surface of the brain. Neither was any constant relation noted between the severity of the reaction, on the one hand, and the anatomic portion of the brain, the amount of free blood or the proximity to the source

21. Martland, H. S.: Spontaneous Subarachnoid Hemorrhage and Congenital "Berry" Aneurysms of the Circle of Willis, Am. J. Surg. **43**:10-19 (Jan.) 1939.

22. Ayer, W. D.: So-Called Spontaneous Subarachnoid Hemorrhage: A Résumé with Its Medicolegal Consideration, Am. J. Surg. **26**:143-151 (Oct.) 1934.

23. Weed, L. H.: Studies on Cerebro-Spinal Fluid: III. The Pathways of Escape from the Subarachnoid Spaces with Particular Reference to the Arachnoid Villi, J. M. Research **31**:51-91 (Sept.) 1914.

24. Hassin, G. B.: Notes on the Nature and Origin of the Cerebrospinal Fluid, J. Nerv. & Ment. Dis. **59**:113-121 (Feb.) 1924.

fibrosis and obliteration of the subarachnoid space were noted post mortem; in Merwarth and Freiman's case the hydrocephalus was of the communicating type.

MATERIAL AND METHODS

The material used in this study was selected from a series of 114 cases in which necropsy was performed at the Mayo Clinic from 1922 to 1943 inclusive, in each of which an intracranial aneurysm was noted. To eliminate as far as possible the existence of an unrecognized infection which could account for any meningeal changes, three types of cases were excluded, for the reasons indicated: (1) cases in which the subarachnoid hemorrhage followed trauma to the head, because of the possibility of fracture of the skull and bacterial contamination of the subarachnoid space; (2) cases in which craniotomy, laminectomy or other surgical procedure involving the central nervous system had been performed, as well as a few cases in which a ventriculogram or an air encephalogram had been made, because of the possible effect of oxygen on the meninges, and (3) cases in which a systemic disease, such as active tuberculosis had been present. One case in which the serologic reactions were positive for syphilis was included, but studies of the spinal fluid before and after the subarachnoid hemorrhage showed no evidence of syphilis of the central nervous system. In every case selected an aneurysm was observed rupture of which could reasonably be assumed to be the source of the bleeding. The presence of such a lesion was established as a criterion in order that an unknown, and possibly infected, source of the hemorrhage should not be overlooked. No attempt was made to separate congenital and arteriosclerotic aneurysms. Cases of rupture of mycotic or traumatic aneurysm were not included. Of the 114 cases, 53 met all the aforestated requirements.

As controls, 26 cases were selected in which death resulted from disease unrelated to the central nervous system, in which there had been no symptoms suggesting disease of the central nervous system and in which no changes in the brain or the spinal cord were noted at necropsy. These cases were chosen in such a way that the age and sex distributions were proportionately the same as those in the 53 cases of subarachnoid hemorrhage.

From four to nine microscopic sections were studied in every case. As a rule, sections were taken from the area of maximal hemorrhage near the ruptured aneurysm, at the base of the brain, over the convexity of the cerebral hemispheres and from the spinal cord. The tissues were stained with hematoxylin and eosin, Mallory's phosphotungstic acid hematoxylin, the Mallory-Heidenhain and Van Gieson stains and the berlin blue stain for iron.

The duration of the hemorrhage prior to death was necessarily based on clinical judgment, but in nearly every case the onset was sufficiently dramatic to leave little question as to when the first rupture took place. The patients had survived various lengths of time, from a few minutes to six months. One patient had died ten years after the rupture, of an unrelated disease, and another had died of a recurrent subarachnoid hemorrhage twelve years after the original hemorrhage. The youngest patient was 18 and the oldest 84 years of age at death. The average age was 49.4 years. In the majority of cases (33) the hemorrhage had

occurred between the ages of 40 and 60. The average age in this group was about 10 years higher than that in most of the reported series of cases of spontaneous subarachnoid hemorrhage.[18] On the other hand, the average age in the fatal cases in the series reported by Richardson and Hyland [19] was 50, and the evidence in the present series tends to confirm the impression of these authors that the prognosis becomes worse with advancing years.

None of the reports in the literature shows any consistent preponderance of patients of either sex. Of the present series of 53 patients, 30 were males and 23 females. The slightly greater incidence (56.6 per cent) of the condition in men is not considered significant.

ASSOCIATED PATHOLOGIC CONDITIONS

In 7 cases necropsy was limited to the head. In the 46 cases in which complete necropsy was performed two associated pathologic conditions stood out. The heart was hypertrophied in 24 instances, this observation offering confirmation of the clinically noted frequent occurrence of hypertension among patients with spontaneous subarachnoid hemorrhage. In 23 cases one or more congenital defects were present. These included ectopic adrenal, pancreatic or splenic tissue, duplication of the ureter, Meckel's diverticulum and malrotation of the colon. This relation has been noted by many investigators and substantiates the hypothesis first presented by Eppinger [20] that intracranial aneurysms develop from congenital defects.

Associated Intracerebral and Intraventricular Hemorrhage.—In 25 cases the subarachnoid hemorrhage was unaccompanied by bleeding into the substance of the brain or into the ventricles. In 26 other cases there was associated intracerebral hemorrhage, and in 20 of these cases the blood had broken through the ependyma and formed clots in the ventricles. In 2 cases of subarachnoid without intracerebral hemorrhage the intraventricular fluid was slightly blood stained, but in every instance in which there was clotted blood in the ventricles an associated intracerebral hemorrhage was present.

18. Neal, J. B.: Spontaneous Meningeal Hemorrhage, J. A. M. A. **86**:6-8 (Jan. 2) 1926. Russel, C. K.: Spontaneous Subarachnoid Haemorrhage, Canad. M. A. J. **28**:133-140 (Feb.) 1933. Tucker, J.: Spontaneous Subarachnoid Hemorrhage: A Brief Review of Fifty Consecutive Cases, Cleveland Clin. Quart. **7**:152-157 (April) 1940. Symonds.[4]

19. Richardson, J. C., and Hyland, H. H.: Intracranial Aneurysms: A Clinical and Pathological Study of Subarachnoid and Intracerebral Haemorrhage Caused by Berry Aneurysms, Medicine **20**:1-83 (Feb.) 1941.

20. Eppinger, cited by Forbus, W. D.: On the Origin of Miliary Aneurysms of the Superficial Cerebral Arteries, Bull. Johns Hopkins Hosp. **47**:239-284 (Nov.) 1930.

An outstanding feature of the reaction at every stage was the considerable variation in the appearance of different portions of the brain, and even in different parts of the same microscopic section. In some locations the cells were exclusively polymorphonuclear leukocytes; in others, entirely lymphocytes, and in still others the various cell types were diffusely mixed.

Death in Seven Days.—By the end of a week the polymorphonuclear cell reaction had subsided. In no case in which the patient lived longer than seven days were polymorphonuclear leukocytes seen unless there had been fresh bleeding during the week before death. The intensity of the cellular reaction was at its peak and was

inent along the parasagittal portions of the cortex and over the pons, medulla and spinal cord than elsewhere. However, in a given portion, this physiologic increase in fibrous tissue is diffusely equal in amount and never, in my experience, passes from pia to arachnoid to obliterate the subarachnoid space. If patients lived more than ten days after subarachnoid hemorrhage, pathologic fibrosis was never excessive, and the fibrous tissue was rarely thicker than the maximum amount present in the meninges of elderly control subjects. The fibrosis following subarachnoid hemorrhage, however, differed in three significant respects from that seen in the controls: First, it was observed characteristically
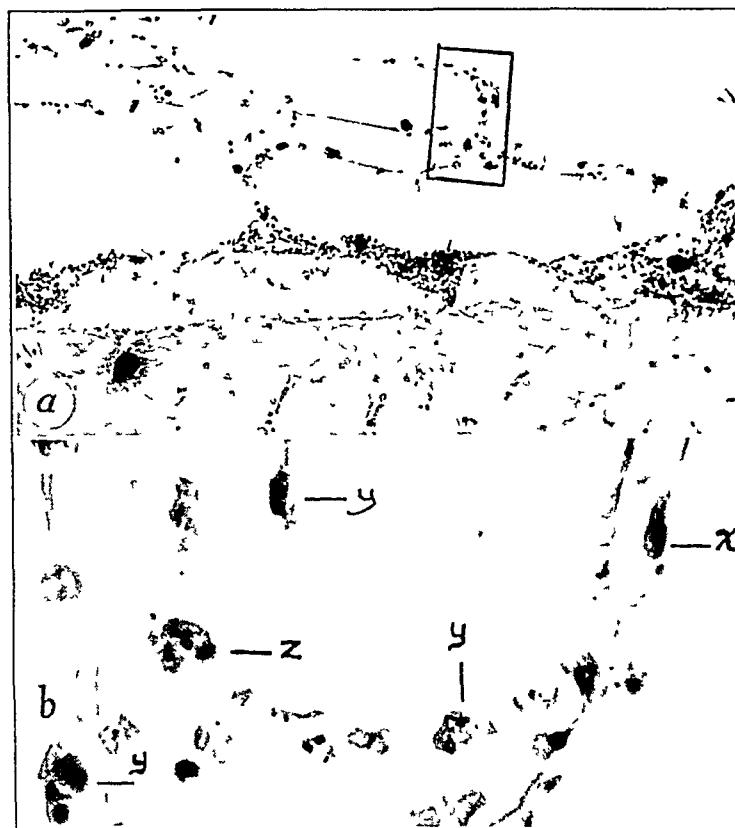
Fig. 3—Lining cells of the arachnoid trabeculae, showing mesothelial cell activity. (*a*) Pigment, red blood cells and debris are trapped in the meshes of arachnoid trabeculae which traverse the subarachnoid space (× 95). (*b*) Higher magnification (× 575) of the blocked area indicated in *a*. Here, *x* indicates a resting lining cell; *y*, various stages of swelling of the lining cells, some of which are phagocytic while still attached to the trabeculae, and *z*, a lining cell which has broken off as a free phagocyte. Several whole red blood cells can be seen in the cytoplasm.

composed about equally of lymphocytes and phagocytes (fig. 4). Pigment and iron were increased in amount, and intact red blood cells still could be identified.

Death in Ten Days.—At this stage there first appeared definite fibrosis in the leptomeninges. The amount of fibrous tissue in the pia-arachnoid of normal persons varies tremendously with the age of the patient and with the portion of the brain examined. Fibrosis is increasingly evident with advancing years and is more prom-

in contact with blood in the subarachnoid space; second, the areas of fibrosis were patchy, being dense in some areas and slight or absent in adjacent parts; and, third, in the end stage, when the blood had disappeared from a given area, the fibrosis was seen to bind pia to arachnoid (fig. 5 *a* and *b*) or pia to pia in a sulcus, and thus to obliterate the subarachnoid space. The fibrosis was noted with about equal frequency in various parts of the brain and appeared as commonly over the surface of the

of the hemorrhage, on the other. After about four hours an outpouring of lymphocytes was noted, and these cells, like the polymorphonuclear leukocytes, were first seen around the pial vessels, this occurrence suggesting that both types of cells enter the meninges from the blood vessels (fig. 2).

Death in Sixteen to Thirty-Two Hours.—Both types of leukocytes increased in number and were more diffusely distributed through the pia-arachnoid at this stage than in the four to sixteen hour stage. The reaction was still predominantly polymorphonuclear. At no time, however, was the response of the polymorphonuclear cells comparable in intensity to that seen in a case of acute purulent bacterial meningitis.

It was during this interval, approximately twenty-four hours after the hemorrhage, that
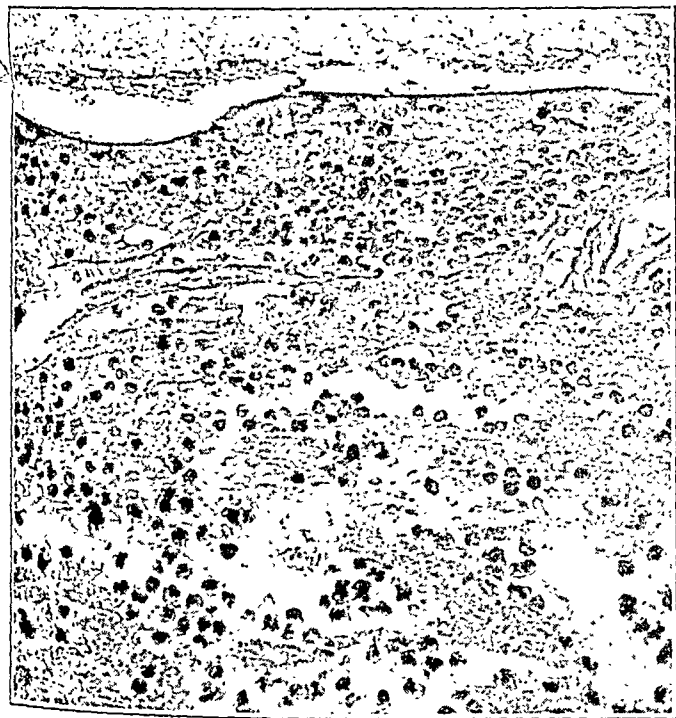
Fig. 1.—Polymorphonuclear leukocyte response to subarachnoid bleeding in the meninges of a patient who had survived five days. Large numbers of polymorphonuclear leukocytes, mixed with degenerating blood, can be seen scattered through the subarachnoid space. × 275.

the mesothelial cells which line the borders of the subarachnoid space and the surface of the arachnoid trabeculae began to take part in the reaction. Normally flat, elongated cells, they now became swollen, rounded and actively phagocytic. This phagocytic tendency was well developed in mesothelial cells which were still attached to the arachnoid or to its trabeculae. Cells often could be traced in all stages of change, from their quiescent state through the phases of their swelling and becoming phagocytic, to their final breaking away from the trabeculae and becoming free cells. Coincident with these changes in the mesothelial cells was

the appearance of large numbers of active phagocytes in the subarachnoid space, and the relationship between these free phagocytes and the mesothelial cells cannot be disputed.

During this period was noted the first evidence of breakdown of blood, in the appearance of brown pigment and iron. The pigment and iron occurred both free in the subarachnoid space and within the cytoplasm of polymorphonuclear leukocytes and phagocytes.

Death in Three Days.—During the third day after the accident all cells had increased in frequency of appearance. The polymorphonuclear cell reaction was at its height, but, because of the rapid increase in the number of lymphocytes and phagocytes, the polymorphonuclear leuko-

Fig. 2.—Perivascular collections of lymphocytes around pial blood vessels in the mouth of a sulcus in the parietal cortex of a man aged 51. Two vessels are visible, with many lymphocytes in the adjacent subarachnoid space. × 275.

cytes now formed less than half the cellular element in the fairly intense meningitic reaction. The original perivascular arrangement of the leukocytes in the meninges could no longer be detected except in rare instances. The activity of the mesothelial cells and the occurrence of free mononuclear phagocytes were more evident. The mesothelial cells were extremely active and often contained within their cytoplasm several whole red blood cells, bits of pigment and iron and degenerated leukocytes (fig. 3 a and b).

microscopic examination. The most outstanding feature of the reaction at every stage after the immediate diffusion of blood through the subarachnoid space was the irregular, patchy distribution of the cellular and, later, of the fibrotic response.

COMMENT

In view of the signs and symptoms of severe meningeal irritation which usually accompany spontaneous subarachnoid hemorrhage, it would indeed be surprising if there was not microscopic evidence of a reaction in meninges exposed to the blood. Correlation between clinical and pathologic signs during the first few weeks of the illness is fairly close. Much less definite is correlation of the end stage of patchy fibrosis seen in the meninges with the later effects of subarachnoid hemorrhage. Sequelae are not common in this condition; if the patient survives the initial insult, he is faced with the constant threat of recurrence, but as a rule he is not subjected to other severe or permanent ill effects. An exception to this, of course, is the patient whose ruptured aneurysm produces intracerebral, as well as subarachnoid, hemorrhage. Occasionally, also, palsy of one of the cranial nerves is encountered, and this is generally accepted as the result of bleeding into the nerve or its sheath. When such palsy occurs, it is present as a rule from the onset of the illness; it does not develop later in the course, as might be expected if it were the result of scarring and fibrosis around the nerve as this structure passes through the subarachnoid space.

In patients in the younger age group there occurs occasionally an obstructive type of hydrocephalus after subarachnoid hemorrhage, and this may be correlated with obliteration of the cerebrospinal fluid pathways by fibrosis. In this series of cases evidence of hydrocephalus was not present. The patchy nature of the fibrosis makes one hesitate to ascribe to it the ability to interfere significantly with the flow of cerebrospinal fluid, unless fibrosis were to occur in particularly vulnerable spots, such as at the foramens of Magendie and Luschka.

It was noted that among the 8 cases of sudden death in which a past history could be obtained there were no instances of associated intracerebral hemorrhage, although the incidence of intracerebral hemorrhage in the entire series was nearly 50 per cent. This fact, together with the appearance, represented in figure 6, of obliteration of the mouth of a sulcus, suggested the possibilty that fibrosis following an earlier hemorrhage might isolate an aneurysm from the

general subarachnoid space and, at a later rupture, cause the blood to break into the brain substance as the line of least resistance. Investigation of this point showed that this was not necessarily true. The incidence of intracerebral hemorrhage in cases of survival for longer than ten days after the initial subarachnoid hemorrhage was essentially the same as that in cases of death in less than ten days. Ten days was taken as the division point because it was at this time that fibrosis was first seen. Furthermore the incidence of intracerebral hemorrhage was no greater in the cases in which necropsy revealed meningeal fibrosis than it was in the cases in which no fibrosis was seen. Nevertheless, the fact remains that a subarachnoid hemorrhage so severe as to cause sudden death rarely, if ever, produces intracerebral bleeding whereas such bleeding is a common catastrophe later in the course if the patient survives the first few hours. Bagley, likewise, noted that intracerebral hemorrhage usually occurs during
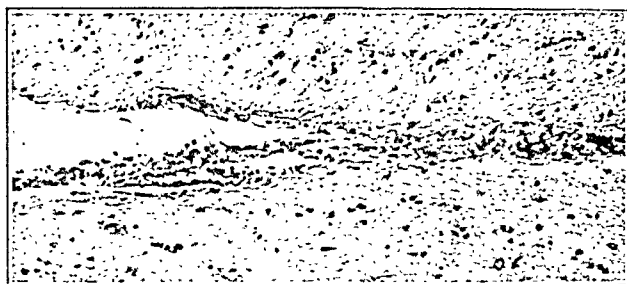
Fig. 6.—Obliteration of the subarachnoid space in a cerebral sulcus. Death occurred three months after the first subarachnoid hemorrhage. The surface of the brain is to the right, beyond the area shown in the photograph. The two adjacent surfaces of pia have been fused as a result of fibrosis. × 90.

the course of a rather mild subarachnoid hemorrhage. It is suggested that the large amount of clotted blood observed at necropsy around the aneurysmal site might serve to isolate the aneurysm from the general subarachnoid space and that the product of any further bleeding would thus be forced into the brain substance. At a later stage organization of the clot and fibrosis might act in the same manner to prepare the way for a subsequent intracerebral hemorrhage. In other words, if an aneurysm is so situated that blood coming from it can rapidly flow through the subarachnoid space, the brain will not be invaded. If, however, the diffusion of blood is obstructed either by the clot of a previous hemorrhage or by fibrosis, intracerebral bleeding is likely to result.

The source of the various elements seen in the previously described reactions is of interest. The perivascular arrangement of both polymor-

hemispheres as it did in the depths of the sulci.

The variation in the degree of fibrosis in different cases was striking. In some cases there were definite changes in every section examined; in others fibrosis was present in only one or two areas, and in nearly half the cases in which survival was for ten or more days no definite fibrotic alteration was seen. The failure to discover fibrosis in such a large percentage of cases was probably due to two factors: First, the patchy nature of the fibrosis was such that five or ten sections taken at random might well miss any fibrotic tissue that was present. Second, the response in the individual case was probably variable; while fibrosis developed in ten days in some cases, the process might take several weeks in others. Of the cases in which the patients had lived seven weeks or longer after the first hemorrhage, postmortem examination in only 1 failed to reveal distinct fibrotic changes.

Fig. 4.—"Lymphocytic meningitis" in a case in which the patient survived eight days after spontaneous subarachnoid hemorrhage. Practically all the cells are lymphocytes. The reaction stops abruptly at the surface of the cortex. The blood vessels are open and show no evidence of being actively involved in the inflammatory process. × 50.

No correlation was observed between the age of the patient and the amount or time of appearance of the fibrosis.

Death in Two Weeks or More.—In all the cases of survival for from two weeks to six months there were recurrent episodes of bleeding. Postmortem examination of the meninges disclosed, in addition to the fibrotic changes previously described, variable amounts of blood pigment, iron, leukocytes and phagocytes, in keeping with the presence of more recent hemorrhages. Activity of the mesothelial cells and the presence of free phagocytes and lymphocytes persisted as long as there was any evidence of blood or of products of breakdown of blood in the subarachnoid space. This is in contrast to

the polymorphonuclear cell response, which subsided in about a week unless further hemorrhage occurred.

In 1 case the patient had survived ten years and had died of an unrelated illness; the meninges were free of blood or cellular reaction, but definite patchy fibrosis was seen. In another case the patient had died twelve years after the primary subarachnoid hemorrhage and twelve hours after a recurrent hemorrhage. Necropsy revealed changes in the pia-arachnoid consistent with those observed post morten in other persons in the series who had died between four and sixteen hours after the vascular accident.
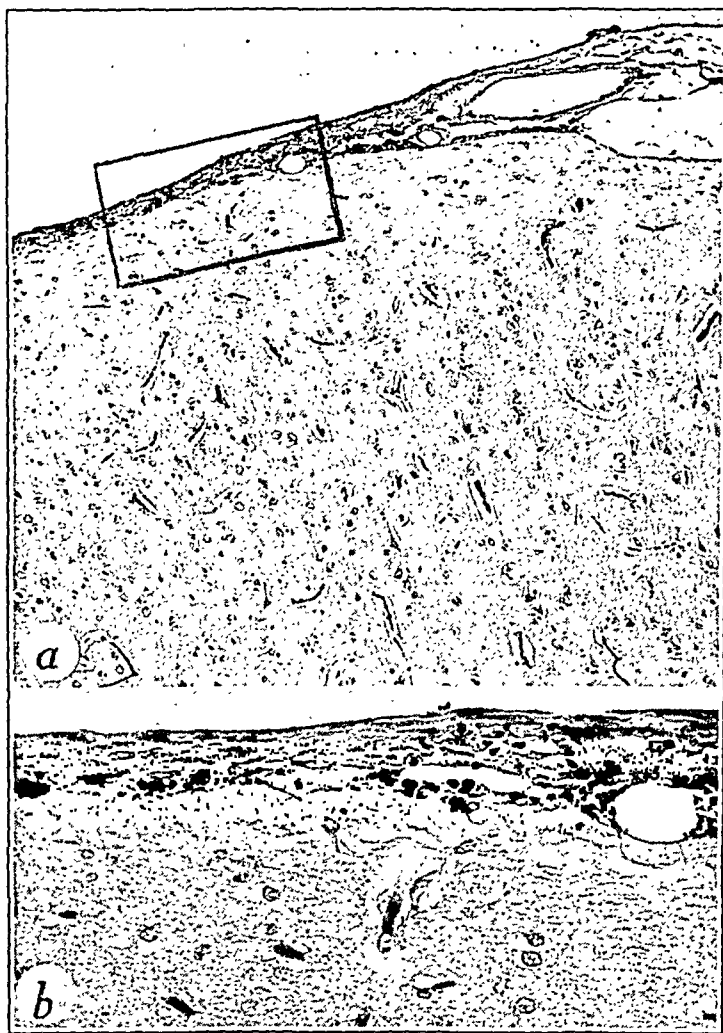
Fig. 5.—Obliteration of the subarachnoid space by fibrosis. Death occurred five and a half months after the initial subarachnoid hemorrhage. (*a*) On the right can be seen the open subarachnoid space, bounded by pia below and by arachnoid above. Toward the left the two membranes approach each other and fuse. × 65. (*b*) The point of fusion, from the blocked area in *a*. The two membranes can no longer be identified in the solid sheet of fibrous tissue. × 200.

In addition, evidence of the woman's primary hemorrhage persisted in the form of fibrosis.

At no time were changes noted in the blood vessels of the pia. The existence of thrombosis or of reactive arteritis with obliteration of the lumen, such as is seen with tuberculous meningitis, was considered theoretically possible, but no evidence for this was forthcoming from

An attempt was made to determine the effect, if any, of therapeutic spinal drainage on the meningeal response to blood. Unfortunately, in no case did the patient receive what might be considered intensive spinal drainage: The greatest number of lumbar punctures done in any single case was nine, in a period of sixteen days; the largest volume of spinal fluid removed was 119 cc., in eight punctures over a period of twenty-one days. The series was divided into three groups on the basis of the amount of spinal drainage, and the meningeal reaction in each group was compared with that in the other groups. Group A was composed of cases in which not more than one lumbar puncture had been done and less than 15 cc. of spinal fluid had been removed. Group C consisted of cases in which five or more punctures had been done and a total of 50 cc. or more of spinal fluid had been removed. Group B was intermediate between groups A and C. No significant difference in the groups was noted with respect to the amount of blood, pigment and iron, the leukocytic response, the activity of the mesothelial cells or the formation of phagocytes. Of the cases in group A (drainage not established), in which the patients had survived long enough for fibrosis to develop, the amount of fibrous tissue in the meninges had increased in 55 per cent. Of the cases in group B fibrosis was observed in 36 per cent, and of the cases in group C, this change was noted in only 25 per cent. While far from conclusive, these figures suggest that removal of the blood by spinal drainage decreases the incidence of permanent meningeal scarring.

The controversy as to the benefits or dangers of therapeutic spinal drainage in cases of subarachnoid hemorrhage can be settled only by consideration of many factors. The effect of blood on the meninges is but one phase of the entire problem. The fact that blood is not well tolerated by the meninges, as evidenced by the transient cellular reaction and permanent fibrosis, suggests strongly that if it can be done safely, removal of as much blood as possible by spinal drainage will lessen the severity of the symptoms of meningeal irritation in a case of subarachnoid hemorrhage.

CONCLUSIONS

1. Autogenous blood in the subarachnoid space is not well tolerated by the leptomeninges in man.

2. The meningeal reaction to blood is evident within two hours of the hemorrhage and begins as an outpouring of polymorphonuclear leukocytes, followed by the appearance of lymphocytes and large mononuclear phagocytes derived from the mesothelial lining cells of the arachnoid.

3. This cellular reaction is transient and persists only as long as blood, or products of breakdown of blood, are demonstrable in the subarachnoid space.

4. Permanent effects occur in the form of patchy fibrosis of the pia-arachnoid, with obliteration of the subarachnoid space. This can be demonstrated only after the blood has been present ten days or longer.

5. From this study, no conclusion can be drawn as to the effect on this meningeal reaction of drainage of bloody cerebrospinal fluid by repeated lumbar punctures.

6. Rupture of an intracranial aneurysm is capable of producing sudden death. Patients suffering from this accident rarely, if ever, have an associated intracerebral hemorrhage, although intracerebral bleeding is common among persons who survive the immediate insult, only to succumb hours or days later.

7. An intraventricular hemorrhage sufficient to produce clotted blood in the ventricles will not occur after rupture of an intracranial aneurysm unless an associated intracerebral hemorrhage exists.

The Mayo Clinic.

phonuclear leukocytes and lymphocytes during the early stages of their appearance points to a hematogenous origin, the cells possibly entering the meninges and the subarachnoid space by direct passage through the walls of the pial vessels. The coincident appearance of activity of mesothelial lining cells and of free mononuclear phagocytes in the cerebrospinal fluid and the meninges suggests the derivation of the

probably manifold. Normally, fibroblasts can be seen in both the pia and the arachnoid, and these presumably contribute to the organization of clotted blood in the subarachnoid space. Moreover, in the early stages of organization occasionally evidence of the laying down of fibroblasts and collagen fibers can be seen, not only at the periphery of the clot but along the surfaces of the many trabeculae enmeshed in
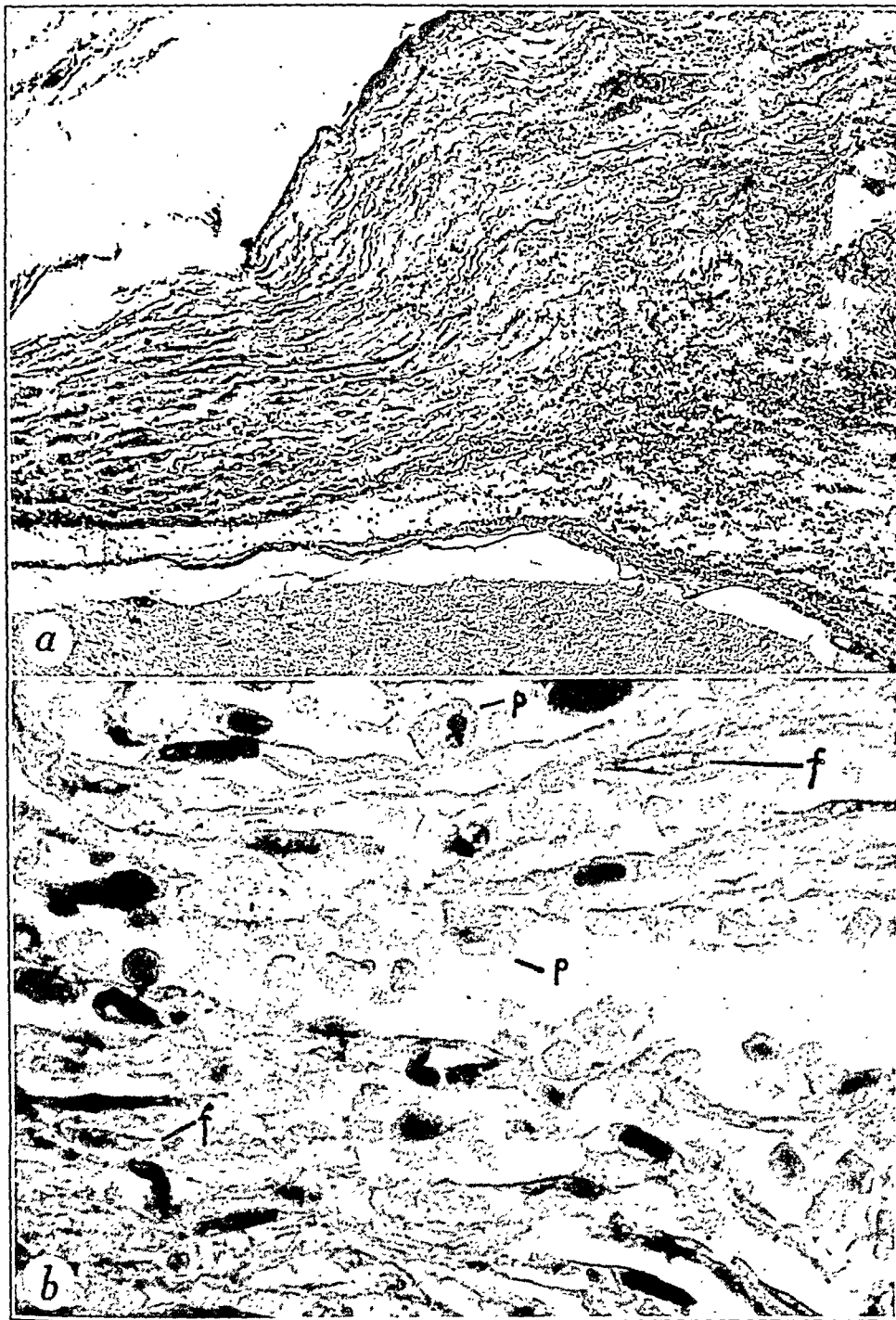
Fig. 7.—Organization of subarachnoid hemorrhage. (a) Many delicate strands of fibrous tissue can be seen passing through the blood parallel to each other and to the surface of the arachnoid. Mallory-Heidenhain stain; × 50. (b) A higher magnification (× 800) of the arachnoid trabeculae in the midst of an area of subarachnoid blood. Individual fibroblasts (f) can be seen in close proximity to the trabeculae. Fully developed phagocytes are indicated by p. Hematoxylin-eosin stain.

latter cells from the former. This is confirmed by the observation of phagocytosis in the mesothelial cells before they lose their attachment to the arachnoid trabeculae, as well as by the presence of cells in all stages of transition, from quiescent lining cells to free phagocytes laden with debris. The origin of the fibroblasts is

it (fig. 7 a and b). The potentialities of the mesothelial cells have been emphasized by Weed, and their ability to form phagocytes has been discussed. That they may also contribute to the formation of fibroblasts is suggested by the procedure of organization outward from the individual trabeculae.

pulsations in the brain which determine the rhythm arise as the result of synchronized activity of the individual neurons. Abnormalities consist of a decrease or an increase in these pulsations outside a given range of frequency and amplitude. Psychologic activity may alter the basic normal rhythm temporarily, but so far as is known it does not give rise to any permanent change in rate or amplitude. Permanent or relatively long-lasting activity outside normal limits has been ascribed only to factors of inheritance, injury or infection of the brain and disturbances of cerebral metabolism. Hence the occurrence of such activity most probably indicates an abnormality in the neurophysiology of the cerebral cortex which may be expressed in terms either of synchronization or of individual neuron beat, and correlations may be sought between the electroencephalogram and the behavior in an attempt to cast light on a wider range of etiologic factors pertinent to the behavior. Such is the purpose of the present study.

METHOD

Six lead electroencephalograms were recorded from the 68 patients studied in this series. The monopolar method was used, and electroencephalograms were secured from the occipital, motor and frontal areas of each side with standard amplifiers and an ink-writing oscillograph. All records were taken for at least eighteen minutes.

In order to quantify the data, the scale of classification of Gibbs, Gibbs and Lennox [8] was employed. This method of classification has several advantages: It is possible to obtain a rapid estimate of the type; the classification is based on a single dimension, that of frequency, and the distribution of the various electroencephalographic types has been computed by Gibbs and associates from a sample of 1,000 neurologically screened normal subjects. The scale is shown in figure 1 of their article.[8]

The correspondence between the ratings made by one of us (J. R. K.), who secured and analyzed all the records, and the ratings of Dr. F. A. Gibbs was obtained by a rereading of records which he loaned us. The agreement was 97 per cent. In no case was there disagreement with respect to classification within the normal or the abnormal range, the nonagreement occurring only with respect to classification within the normal frequency limits and involving half-cycle frequencies.

The patients used in this study were carefully chosen on the basis of the completeness of the psychiatric, neurologic, physical and psychometric examination and the social history. In all cases the histories were given by the parents, a relative or some person who knew the patient well. The majority of the histories were corroborated by outside investigation.

From the social histories we chose a number of factors which we had previously found [9] to be important in establishing relations with the electroencephalographic records. These factors fell under two heads: the family history and a personal history of illness or injury. The family history was called positive if there was clear ancestral evidence of (1) psychosis, (2) maladjusted personality, (3) alcoholism or (4) epilepsy. The factors in the personal history of the patient which were chosen as significant included (1) premature birth, (2) birth injury or possible birth injury, (3) anoxia
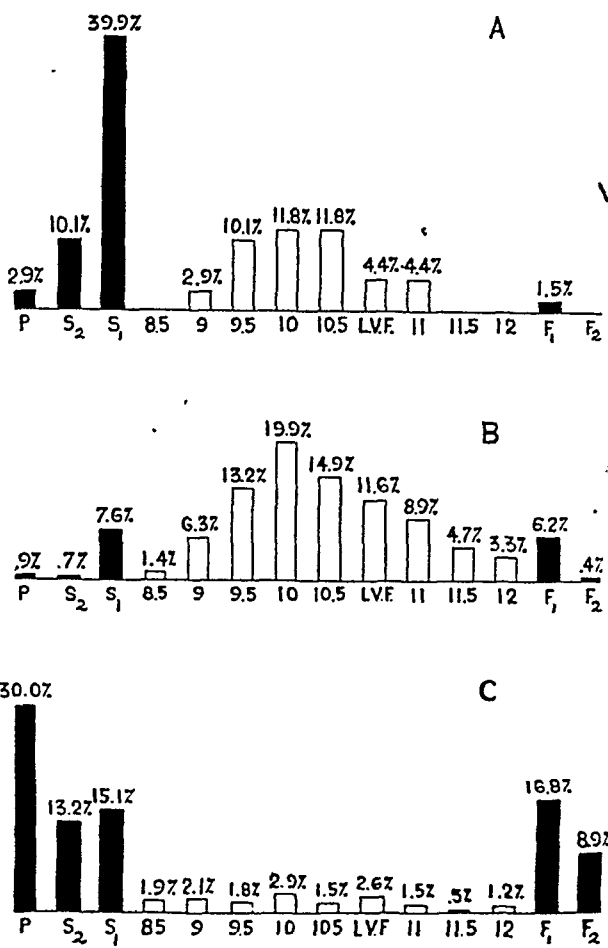
A, percentage distribution of electroencephalographic types for 68 patients with a condition diagnosed as psychopathic personality. At the bottom of each graph, *P* (paroxysmal) includes the various seizure discharges, the first three and the last two strips in figure 1 of Gibbs and associates [8]; S_2 indicates very slow activity; S_1, slightly slow activity; *LVF*, low voltage fast activity; F_1, slightly fast activity, and F_2, very fast activity. Categories shown in black are considered abnormal. The numbers indicate the percentages of the total series. *B*, percentage distribution of electroencephalographic types for 1,000 adult controls. The symbols are the same as those in *A*. *C*, percentage distribution of electroencephalographic types for 660 adult epileptic patients. The symbols are the same as those in *A*.

at birth or after birth, (4) *injury to the head resulting in prolonged unconsciousness or delirium*, (5) *severe febrile illness complicated by delirium and (6) convulsions in infancy*. With none of the patients was it suspected that the personal history of illness or

8. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: Electroencephalographic Classification of Epileptic Patients and Control Subjects, Arch. Neurol. & Psychiat. 50:111-128 (Aug.) 1943.

9. Gottlieb, J. S.; Knott, J. R., and Ashby, M. C.: An Electroencephalographic Evaluation of Primary Behavior Disorders in Children, Arch. Neurol. & Psychiat., to be published.

ELECTROENCEPHALOGRAPHIC EVALUATION OF PSYCHOPATHIC PERSONALITY

CORRELATION WITH AGE, SEX, FAMILY HISTORY AND ANTECEDENT ILLNESS OR INJURY

LIEUTENANT (jg) JOHN R. KNOTT, H-V(S), U.S.N.R.*

AND

JACQUES S. GOTTLIEB, M.D.

IOWA CITY

In a previous report[1] it was indicated that adults who exhibited certain personality deviations presented abnormalities in the electroencephalogram. Of 44 patients with a condition diagnosed as "psychopathic personality," 23, or 52 per cent, had electroencephalograms which did not meet our criteria of normal. Several other investigations have been made independently, and all have revealed a similar relation. Hill and Watterson[2] reported that 48 per cent of 151 patients with a disorder diagnosed as "psychopathic personality" had abnormal electroencephalograms. Silverman,[3] in a study of the more extreme and dangerous criminal psychopathic personalities, found that 80 per cent of 75 patients exhibited abnormal or borderline abnormal tracings. In view of the essential agreement of these three reports, the problem of the meaning of this relation arises.

One of the inherent difficulties in a study of this kind is the inability to define meaningfully the concept "psychopathic personality." Maughs,[4] in his historical review, pointed out the continuous changes in the concept, and Preu[5] emphasized the negative side in arriving at a diagnosis. Unfortunately, no symptoms are considered specific for or pathognomonic of the psychopathic personality. The term is applied to various inadequacies or deviations of the personality, when they are not due to mental deficiency, structural disease of the brain, epilepsy or definite mental disease (i. e., psychoses and psychoneuroses), which prevent socially acceptable adaptation of the person to his environment. This concept is so broad that the cross sectional picture may include symptoms produced by encephalitides, encephalopathies, epileptic states and postpsychotic defective states, as well as similar symptoms due to psychologic factors. Longitudinal studies and the anamnesis allow many persons to be categorized in relation to the important etiologic factors and thus excluded. However, there remains a large group of persons whose personality deviations have been maintained from early life and who do not fall under any of the specific categories aforementioned, according to present diagnostic criteria, and yet who deviate significantly in their personality adjustment. The tendency to emphasize the psychogenic etiologic aspects to the exclusion of genogenic, histogenic and chemogenic factors has led some authorities to change the diagnostic term for the defect presented by these persons to "neurotic character."[6] Unfortunately, consideration of the psychogenic factors does not completely solve the problem presented by such patients, although much pertinent information has been obtained, but simply emphasizes one of the many etiologic aspects involved.

The occurrence of a high incidence of abnormal electroencephalograms in this group presents one avenue of study to the manifold relationships. Gerard and Libet[7] stated that the electrical

* On leave of absence from the State University of Iowa.

From the Iowa State Psychopathic Hospital and the State University of Iowa College of Medicine.

1. Knott, J. R., and Gottlieb, J. S.: The Electroencephalogram in Psychopathic Personality, Psychosom. Med. 5:139-141, 1943.

2. Hill, D., and Watterson, D.: Electroencephalographic Studies of Psychopathic Personalities, J. Neurol. & Psychiat. 5:47-65, 1942.

3. Silverman, D.: Clinical and Electroencephographic Studies on Criminal Psychopaths, Arch. Neurol. & Psychiat. 50:18-33 (July) 1943.

4. Maughs, S.: A Concept of Psychopathy and Psychopathic Personality: Its Evolution and Historical Development, J. Crim. Psychopath. 2:329-356 and 465-499, 1941.

5. Preu, P. W.: The Concept of Psychopathic Personality, in Hunt, J. M.: Personality and the Behavior Disorders, New York, The Ronald Press Co., 1944.

6. Alexander, F.: The Neurotic Character, Internat. J. Psychoanal. 2:292-311, 1930.

7. Gerard, R. W., and Libet, B.: The Control of Normal and "Convulsive" Brain Potentials, Am. J. Psychiat. 96:1125-1152, 1940.

515

electroencephalograms, while of the latter, 5 (83 per cent) had abnormal electroencephalograms and only 1 (17 per cent) had a normal electro-encephalogram. When this difference in the distribution of abnormalities was treated with the chi square (χ^2) test, it was found that the difference was significant between the levels of confidence of 5 and 2 per cent. Therefore, one

TABLE 3.—*Analysis of the Electroencephalogram with Relation to a Positive Family History*

Family History	Electro-encephalograms	
	Abnormal	Normal
Psychosis only	3	1
Psychosis and maladjusted personality	1	5
Psychosis and alcoholism	..	3
Psychosis and epilepsy	1	..
Totals	5	9
Maladjusted personality	9	4
Maladjusted personality and psychosis	1	5
Maladjusted personality and alcoholism	3	..
Maladjusted personality and epilepsy	2	..
Totals	15	9
Alcoholism	4	2
Alcoholism and psychosis	..	3
Alcoholism and maladjusted personality	3	..
Totals	7	5
Epilepsy	1	
Epilepsy and psychosis	1	
Epilepsy and maladjusted personality	2	
Total	4	

may reject the hypothesis that the difference between the distributions was due to chance.

When the distribution of abnormalities for the patients with a completely negative history were compared with the distributions for the patients who had only a positive family history, it was found that the chi square test yielded a level of confidence of approximately 10 per cent. This suggests that the difference in the distribution may not be the result of chance factors, although the hypothesis needs further test. When the factor of illness and injury alone was studied and the distributions of electroenceph-alograms for patients with a positive history were compared with the distributions for the patients with a negative history, the chi square test yielded, again, a level of significance of approximately 10 per cent. Again, one may merely conclude that the probability that this difference in the distributions was due to chance is not great, but one needs further data for con-firmation. Apparently, therefore, when the two factors of the family and of the personal history operate together, the differences are more reli-able than when the factors operate separately.

Since there seems to be a relation between the factors which we have investigated and the

abnormalities in the electroencephalograms, it becomes pertinent to break down our concept of a positive family history into its component factors (table 3) and to break down our con-cept of antecedent illness and injury into its component parts (table 4).

From a study of table 3 one can surmise that the factors of maladjusted personality and epi-lepsy are probably of greater importance in re-lation to the abnormal electroencephalogram than are the factors of psychosis and alcoholism, for the ratios of abnormal to normal electro-encephalograms in the first two categories are essentially 2 to 1.

It is impossible to tell from table 4 whether any one factor of illness or injury is of greater importance than another because the number of cases in each category is too small.

COMMENT

In another study on the relation of the electroencephalographic pattern and primary be-havior disorders in children,[9] the data strongly suggested that abnormal electroencephalograms were obtained for a high percentage of patients

TABLE 4.—*Analysis of the Electroencephalogram with Relation to Illness and Injury*

Illness and Injury	Electro-encephalograms	
	Abnormal	Normal
Prematurity	..	1
Prematurity and head injury	1	
Totals	1	1
Birth injury	1	..
Birth injury and convulsions	..	1
Totals	1	1
Head injury	1	1
Head injury and prematurity	1	..
Head injury and convulsions	1	..
Totals	3	1
Severe illness	5	2
Convulsions	1	..
Convulsions and birth injury	..	1
Convulsions and head injury	1	..
Totals	2	1
Anoxia (carbon monoxide poisoning)	1	
Birth injury and anoxia	1	

who had either a positive family history or a history of antecedent illness or injury, and for a significantly smaller percentage of patients for whom neither factor appeared. These results are consistent with the data reported here for the relation of the electroencephalogram to the psychopathic personality. The hypothesis, then, seems warranted that the abnormality evident

injury played a part in the current difficulties of behavior. All patients who had positive neurologic signs or for whose personality variations it seemed likely that previous illness or injury could be held responsible were excluded at the outset of the investigation. No records obtained during or after hyperventilation were used.

DATA

The distribution of the electroencephalograms of the 68 patients, classified according to the scale of Gibbs, Gibbs and Lennox, is shown in the figure, A. This distribution may be compared with that for 1,000 normal controls (figure, B) and that for 660 adult epileptic subjects (figure, C), recorded by them.[8]

The figure clearly indicates a difference in the form of the distribution curves for these three groups of subjects. The distribution for the psychopathic personalities was radically different than that for the epileptic adults, a fact which

males, a ratio of approximately 2 to 1. The differences in the distributions of normality and abnormality with relation to sex, however, were not statistically significant, and one need not reject the hypothesis that the electroencephalographic patterns show no significant sex difference.

Table 2 presents an analysis of the electroencephalograms with relation to antecedent illness, injury and/or family history. Thirty-three patients (48 per cent) had a positive family history; 11 patients (16 per cent) had a history of antecedent illness or injury uncomplicated by a positive family history; 6 patients (9 per cent) had both a positive family history and a significant antecedent illness or injury, and 18 patients (27 per cent) had a negative family history and no antecedent illness or in-

TABLE 1.—*Analysis of the Electroencephalogram* * with Relation to Age and Sex

Ages, Yr.	Male					Female					Totals
	P	S²	S¹	N	F¹	P	S²	S¹	N	F¹	
16-17	..	2	6	4	..	..	1	2	3	..	18
18-19	..	..	2	1	..	..	1	1	1	..	6
20-21	..	..	1	1	1	1	..	2	..	..	6
22-23	..	1	..	..	..	..	1	1	..	..	3
24-25	1	..	3	..	..	..	..	..	1	..	5
26-27	..	..	1	4	..	..	..	..	2	..	7
28-29	..	..	..	1	..	..	..	..	..	..	1
30-34	..	..	1	5	..	..	1	..	1	..	8
35-39	..	..	1	2	..	..	..	1	..	..	4
40-44	..	..	1	1	..	..	..	2	1	..	5
45-49	..	..	..	1	..	..	..	..	1	..	2
50-54	..	..	1	1	..	..	..	..	..	..	2
55-59	..	..	..	..	..	..	..	..	..	..	..
60 and older	..	..	1	..	..	..	..	..	..	..	1
	1 (2%)	3 (7%)	18 (41%)	21 (48%)	1 (2%)	1 (4%)	4 (17%)	9 (37%)	10 (42%)		68

* In accordance with the Gibbs classification, in this table and in table 2, P indicates paroxysmal; S² great amount of activity slower than 8½ per second in any lead; S¹, moderate amount of activity slower than 8½ per second in any lead; F¹, moderate amount of activity faster than 12 per second, and N, normal activity.

suggests that these two clinical groups represent two different electroencephalographic populations. Both differ from the neurologically normal electroencephalographic population. Twenty-seven (73 per cent) of the 37 patients had abnormal records classified as slightly slow (S¹) ("moderate amount of activity slower than 8.5 per second in any lead" [8]).

In further treatment of the data, records falling outside the normal range of frequencies (8.5 to 12 per second, and including low voltage fast activity) were called "abnormal," and in all statistical evaluations that unit was compared with the "normal" (all frequencies so covered in the Gibbs scale).

Table 1 presents an analysis of the electroencephalograms in relation to age and sex. With respect to age no statistically significant difference appeared, and it may be assumed that this variable was unrelated to the abnormalities in our sample. Forty-four of the patients were

TABLE 2.—*Analysis of the Electroencephalogram with Relation to Antecedent Severe Illness or Head Injury and Positive Family History*

	Electroencephalograms				
	P	S²	S¹	N	F¹
Positive family history only	..	5 (15%)	14 (42%)	14 (42%)	..
Illness or injury only	..	1 (9%)	6 (54%)	4 (36%)	..
Positive family history and illness or injury	1 (17%)	..	3 (50%)	1 (17%)	1 (17%)
No positive family history or illness	1 (5%)	1 (5%)	4 (22%)	12 (67%)	..
Totals	2 (3%)	7 (10%)	27 (40%)	31 (46%)	1 (1%)

jury. Perhaps the most striking difference was that between the patients with a negative family history and no history of antecedent illness or injury and the patients with both a positive family history and a history of antecedent illness or injury. Of the former, 12 (67 per cent) had normal and 6 (32 per cent) abnormal

INTRACRANIAL PRESSURE IN THE HUMAN SUBJECT AT ALTITUDE

CAPTAIN ERIC W. PETERSON
ROYAL CANADIAN ARMY MEDICAL CORPS

SQUADRON LEADER BASIL S. KENT
ROYAL AIR FORCE VOLUNTEER RESERVE
AND
WILLIAM V. CONE, M.D., F.R.C.S.(C)
MONTREAL, CANADA

It has been specifically stated by various authorities that there is an increase in the intracranial pressure at high altitudes. In view of this assumption, it was proposed to study the effects of altitude on the intracranial pressure in a patient with a large cranial defect. The subject owes his life to the fact that, with dura torn and cerebral substance protruding from the wound, he was fortunate enough to be transported by air to a hospital for specialized neurosurgical treatment. The tremendous size of the cranial defect which resulted and the fact that there was no retraction of the scar made direct and unusual instrumental observations possible. There are conflicting reports in the literature concerning the behavior of intracranial pressure at high altitudes when the subject is breathing oxygen and when he is anoxic. Walsh[1] described the case of a patient with a cranial defect following craniotomy in whom decompression on elevation to an altitude of 28,000 feet (16,900 meters) while he was breathing oxygen resulted in herniation of the overlying scalp to the extent of 1 cm. Walsh and Boothby[2] described an increase of intracranial pressure of about 30 mm. of water on decompression in human subjects breathing oxygen on their being subjected to altitudes of 30,000 feet (18,100 meters). Arm-

strong,[3] using goats, recorded the cerebrospinal fluid pressure on decompression with cisternal punctures and observed that there was an increase in pressure which began at an altitude of 18,000 feet (10,880 meters) and continued up to an altitude of 50,000 feet (30,240 meters). In his experiments he failed to mention the presence of abdominal distention and its influence on intracranial pressure through the increased venous pressure. He recorded an increase amounting to "several inches of water pressure." Bergeret and Giordan,[4] working with dogs, showed increases in intracranial pressure, as well as in venous pressure, when the animals were subjected to simulated high altitudes, and these changes could be reversed by the giving of oxygen, although the altitude was maintained.

Walsh, Walsh and Boothby and Armstrong all reported the appearance of bubbles in the column of fluid filling the manometer on ascent to high altitudes.

CLINICAL REPORT OF A CASE

The patient was accidentally shot when a Sten gun, which he was replacing on the floor, went off. The bullet, at this close range, entered the head just above the left eyebrow and made its exit just over the vertex. The patient was instantly unconscious and could not recall details of the accident. The trauma occurred about thirty-six hours prior to his admission to the hospital.

He was transferred from Nova Scotia, where the shooting occurred, by means of two aircraft, additional short distances being covered by rowboat, truck and ambulance. Because of the severe loss of blood he received two transfusions of plasma in isotonic solution of sodium chloride (500 cc. each) in preparation for transportation. Also, he was given morphine sulfate, ¼ grain (16 mg.), at the beginning of the flight. Evacuation by air was undertaken at an average alti-

1. Walsh, M. N.: Changes in Intracranial Volume on Ascent to High Altitudes and Descent as in Diving, Proc. Staff Meet., Mayo Clin. 16:220, 1941.

2. Walsh, M. N., and Boothby, W. M.: Demonstration of Air Bubbles in Spinal Fluid Under Lowered Atmospheric Pressures Produced in a Low Pressure Chamber, Proc. Staff Meet., Mayo Clin. 16:225, 1941; correction, ibid. 16:304, 1941.

3. Armstrong, H. G.: Aviation Medicine, Baltimore, Williams & Wilkins Company, 1939.

4. Bergeret, P., and Giordan, P.: The Cerebrospinal Fluid Pressure Under the Influence of Atmospheric Depression, J. de physiol. et de path. gén. 36:1050, 1938.

in the electroencephalograms either is inherited as such or is due to illness or injury in childhood which altered the function of cerebral tissue, yet was considered of no clinical significance. The suggestion follows, then, that the category "psychopathic personality," like the category of primary behavior disorders in children, may be further divided into (1) psychopathic personality with normal electroencephalogram and (2) psychopathic personality with abnormal electroencephalogram, the latter being further divisible into a type in which the electroencephalographic abnormality is of genetic origin and a type in which it is related to the cortical damage sustained early in life through illness or injury. It may further be suggested that the genogenic, chemogenic and histogenic factors are of greater etiologic importance than had heretofore been commonly ascribed to them.

Although this hypothesis seems warranted on the basis of the accumulated data, there remain several factors which may complicate it. An abnormal electroencephalogram is not pathognomonic of either psychopathic personality or primary behavior disorders in children, as is easily evident from the electroencephalographic examination of any psychiatric or neurologic population. With various other clinical entities there are associated abnormal waves, although apparently in a lower proportion than with the types of psychopathic personality reported on here, with the exception of epilepsy and known organic entities. It follows, therefore, that the presence of an abnormal electroencephalogram is not indicative of a specific type of deviation of behavior (for example, aggressiveness has been claimed by some investigators [2]), but is merely indicative of an apparently reliable probability that there will be some kind of deviation in behavior.[10] Furthermore, there are persons generally conceded to be "normal" who show general electroencephalographic characteristics falling beyond the present concept of normality. One might wonder whether the "normal" adjustment of these persons is true or superficial

and whether there may in their future be periods of non-normal adjustment.

A likely formulation of these facts suggests that electroencephalographic abnormality (unless it is specific for the epilepsies) is merely an indication of an organism's susceptibility to difficulties in behavioral adjustment. Such persons may possess less elasticity in their neural limits [9] for withstanding the stresses and strains of the adjustment process, their neural limits varying but being dependent on genogenic, histogenic and/or chemogenic factors. It is probable that a significant proportion of the categories of psychopathic personality and primary behavior disorders in children are characterized by neural limits which lead to greater susceptibility, and hence to poorer adaptation in the patient's interreaction with the social environment. Whether there are any specific entities within these groups remains to be determined.

CONCLUSIONS

1. Fifty-four per cent of a series of 68 patients with a condition diagnosed as psychopathic personality, for which no organic cause was suspected, had abnormal electroencephalograms, characterized principally by the presence of slow or very slow waves.

2. When the electroencephalograms were classified according to the Gibbs, Gibbs and Lennox [8] scale and compared with the electroencephalograms of their groups of neurologic normal controls and epileptic patients, the distribution for the patients with psychopathic personality was radically different from the distributions for the other two populations.

3. Age and sex were unrelated to electroencephalographic abnormality.

4. Significantly greater proportions of abnormal electroencephalograms were found when there were both a positive family history (of psychosis, maladjusted personality, chronic alcoholism or epilepsy) and a personal history of cerebral trauma or severe illness than when neither of these factors was present. The statistical significance was not so great when only one of these factors was operating. However, the higher incidence of abnormal electroencephalograms associated with any one of these factors was probably not due to chance.

10. In a preliminary attempt to correlate certain personality characteristics and the electroencephalographic pattern, we were unable to discover any significant relation. Regardless of the dominant traits, abnormalities were about equally distributed in the trait groups. Yet if only one characteristic had been chosen for study in a highly selected population, and the presence of electroencephalograms had been studied in relation to the presence or absence of the trait, it might have been possible to demonstrate such a relation, especially if that trait had entered into the definition of the population.

Dr. F. A. Gibbs loaned us samples of his electroencephalographic records, so that his evaluations could be compared with ours, and granted us permission to use his data on normal controls and epileptic patients.

skull prosthesis was fixed to the patient by means of rubber cement, firmly held in position by means of rubber straps and filled with water, which had previously been boiled. The most dependent outlet was connected to a 2 mm. bore manometer, graduated in centimeters, and the other outlet, to a piece of clamped rubber tubing. Great care was taken to prevent the entrance of any bubbles of air and to obtain a perfect water-tight seal. Certain difficulties were encountered in the construction of this apparatus—a water-tight seal demanded that the Plexiglass dome should be of perfect fit, and special attention had to be paid to the area over the left eye, where a thin rubber dam was cemented to the inner side of the dome; the brass manometer outlets were

formed was held in position with a rubber strap. A couch was arranged transversely across the decompression chamber; a lumbar puncture was made with an 18 gage needle between the third and the fourth lumbar vertebra, and the needle was connected with a manometer.

With the aforementioned apparatus, experiments in the decompression chamber were carried out as follows:

EXPERIMENT 1: The herniometer was fixed in position, and the subject, while breathing oxygen, was taken to an altitude of 30,000 feet (18,100 meters) at the rate of 3,000 feet (1,800 meters) per minute, herniometric recordings being made every 10,000 feet (6,048 meters).
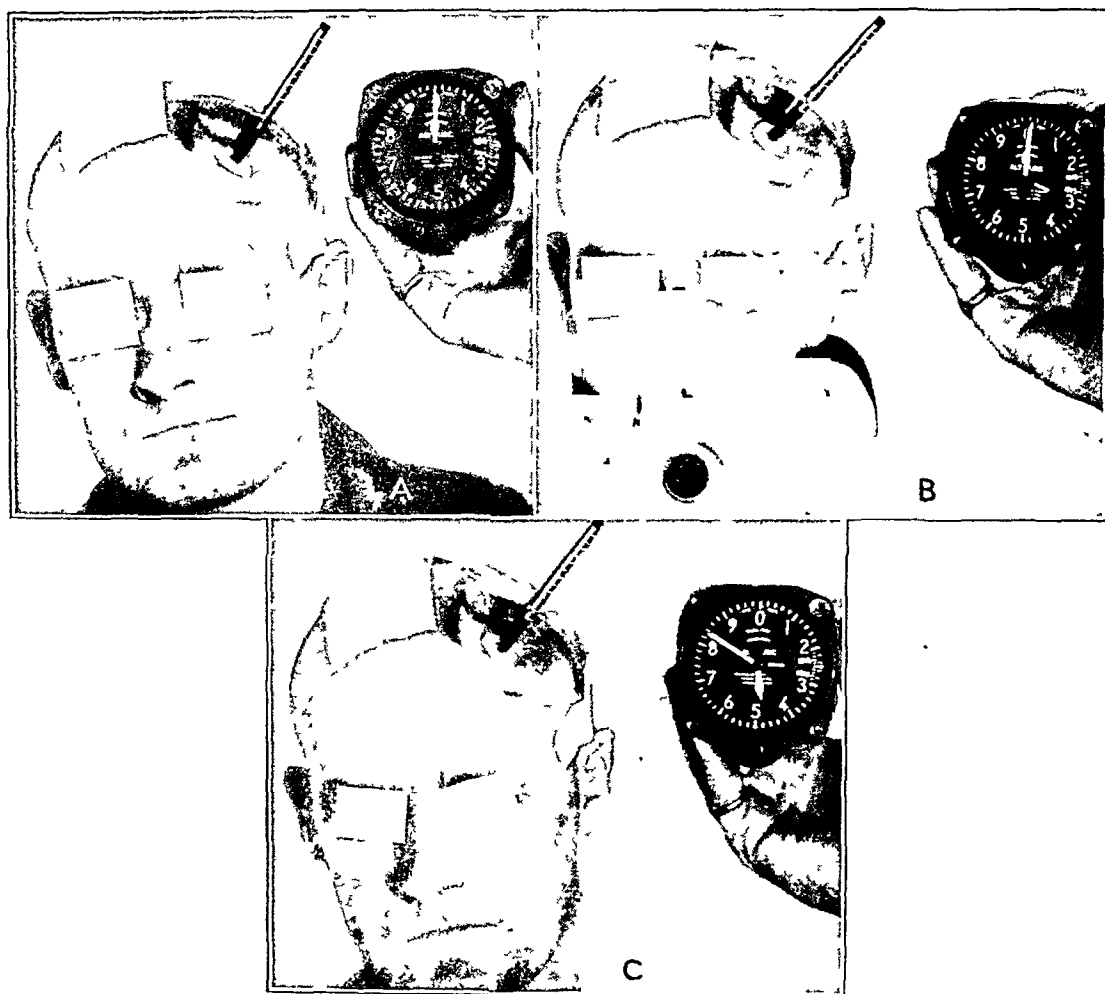
Fig. 3.—*A*, herniometer at ground level; *B*, herniometer at 30,000 feet (18,100 meters), with the subject breathing oxygen (the flash bulb exploded when this picture was taken), and, *C*, herniometer at 25,000 feet (15,320 meters) after the subject had been deficient in oxygen for two minutes and twenty seconds.

sunk flush with the inner side of the dome to prevent the occurrence of air locks around their shoulders.

The plethysmograph thus formed had a capacity of 203 cc. and, because of such a volume of fluid, transmitted impulses with great accuracy (fig. 2).

The efficiency of the apparatus was tested by various methods, with the following results: (*a*) with normal oscillations, 55 mm. of water systolic and 75 mm. diastolic; (*b*) on the subject's coughing, 35 mm. systolic and 180 mm diastolic; (*c*) on his laughing, 35 mm. systolic and 150 mm. diastolic, and (*d*) with light gripping of an object, 45 mm. systolic and 220 mm. diastolic.

Lumbar Puncture.—The cerebral defect was filled completely with rapidly setting plaster, and the cast so

The pressure in the decompression chamber was then dropped to simulate the pressure at 25,000 feet (15,320 meters), and the subject's mask was removed for two minutes and twenty seconds. Descent to ground level was then made, at the rate of 1,000 feet (604 meters) per minute. Photographic recordings of the herniometric readings were obtained at ground level, at 30,000 feet (18,100 meters) while the patient was taking oxygen and at 25,000 feet (15,320 meters) when he was anoxic (fig. 3).

EXPERIMENT 2: With the plethysmograph in place, an ascent to 25,000 feet (15,320 meters) was made with the subject breathing oxygen and in a sitting posture (fig. 2). He remained at this altitude for twenty minutes, and during that time his oxygen mask was removed on

tude of 6,000 feet (3,600 meters). No ill effects due to the flight were observed, and the pulse was recorded as averaging 110 per minute.

Examination on his arrival at the hospital revealed a penetrating wound of the left frontal region of the skull, with tearing of the dura and cerebral laceration. He was very pale and obviously was suffering from the effect of hemorrhage. The red blood cell count was 3,790,000. Clinically, there was right hemiplegia, with
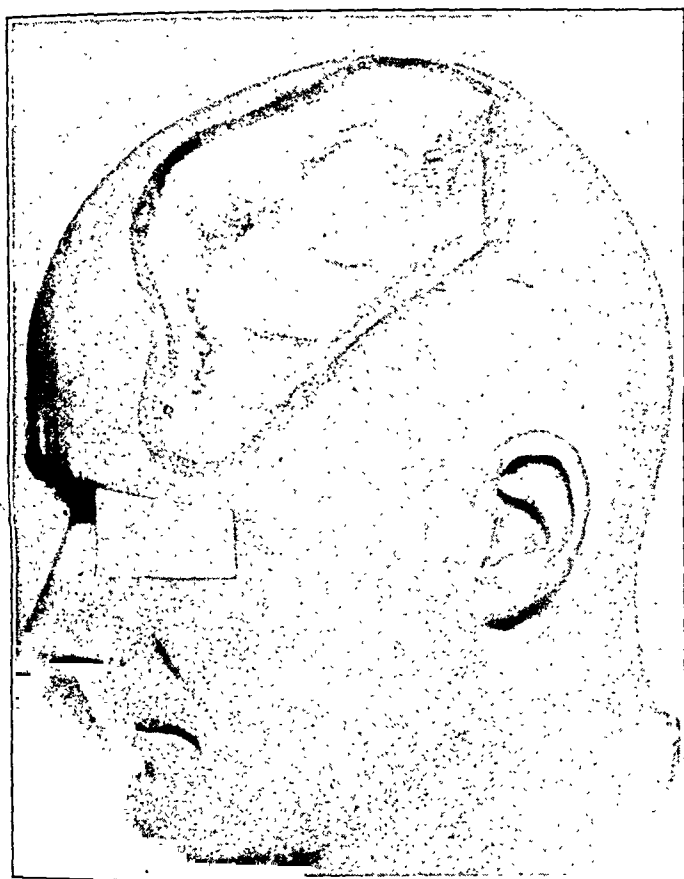
Fig. 1.—Cranial defect outlined to show its extent.

the characteristic reflex changes. The right ear drum was bulging, and there was bluish discoloration of the tympanic membrane.

Damage to the brain and skull was extensive. There was much pulped brain tissue, and large blood clots outlined the bullet's path. Bits of metal and fragments of bone were present in the softened brain. The calvarium was extensively comminuted. Above the wound of entrance, which was cleancut, there was an irregular laceration of the scalp, through which a fragment of bone had apparently been blown. Over the wound of exit, which was large, the laceration of the scalp was wide and irregular.

The damage to the brain extended back beyond the central fissure; though the injury extended deep in the cerebral substance, the ventricle was not opened.

At operation, which was performed immediately on his admission, the scalp and skull were completely debrided, and softened brain substance was irrigated away. Blood clots were also removed. The dura was closed loosely, and a rubber dam drain, brought out by means of a stab wound, was left in the defect made by removal of the damaged brain substance.

An encephalogram made four and a half months later showed that the skin overlying the defect moved out considerably when the ventricles were being filled, and the defect for some time afterward was considerably fuller.

At the time of the present investigation the defect, which measured approximately 16 by 10 by 2.5 cm., was

perfectly healed and freely mobile under stresses of artificially increased intracranial pressure (fig. 1).

METHOD OF INVESTIGATION

Decompression Chamber.—A decompression chamber capable of accommodating twelve persons was used throughout the experiments. Preliminary decompression was carried out with a view to familiarizing the subject with the knack of maintaining the patency of the eustachian tubes and to acquainting him with the unusual surroundings of the chamber, in order to reduce emotional upset to a minimum.

Herniometer.—The light cerebral herniometer constructed consisted of a rubber cylinder, graduated in millimeters, which moved freely through a plastic guide (fig. 3). The apparatus was fixed to the subject's head by means of rubber cement.

The efficiency of the apparatus was tested by various methods which raise the intracranial pressure, with the following readings: (a) normal oscillation due to pulsation of the defect, 1 mm.; (b) with the patient firmly gripping an object, 3 mm.; (c) with the subject "bearing down," 4 mm.; (d) with the subject laughing, 5 to 6 mm.; (e) with application of a small sphygmomanometer cuff to the neck at a pressure of 90 mm. of mercury, 8 mm., and (f) with a postural change of 90 degrees (from 30 degrees feet down to 60 degrees head down) on the x-ray table, 15 mm.

Cranial Plethysmograph.—A plaster cast of the cerebral defect and the surrounding cranium was made, and from it an exact stone copy was constructed. A Plexiglass dome was formed by stretching Plexiglass under steam heat. The principle adopted was to clamp the
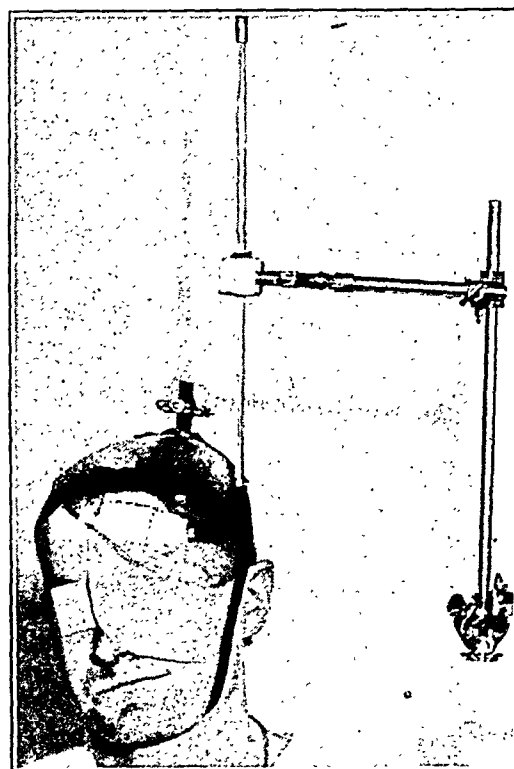
Fig. 2.—Cranial plethysmograph cemented and strapped in position.

Plexiglass firmly on to an iron frame, place the replica of the skull (with defect filled), and with considerable weight on it, vertex downward on the tray thus formed and subject the whole to steam heat at approximately 230 F. The mold obtained was trimmed and drilled for the insertion of manometer connections. A female stone mold was also constructed to prevent any possible loss in shape. Brass manometer insertions were made and sealed flush into the Plexiglass with heat. The rigid
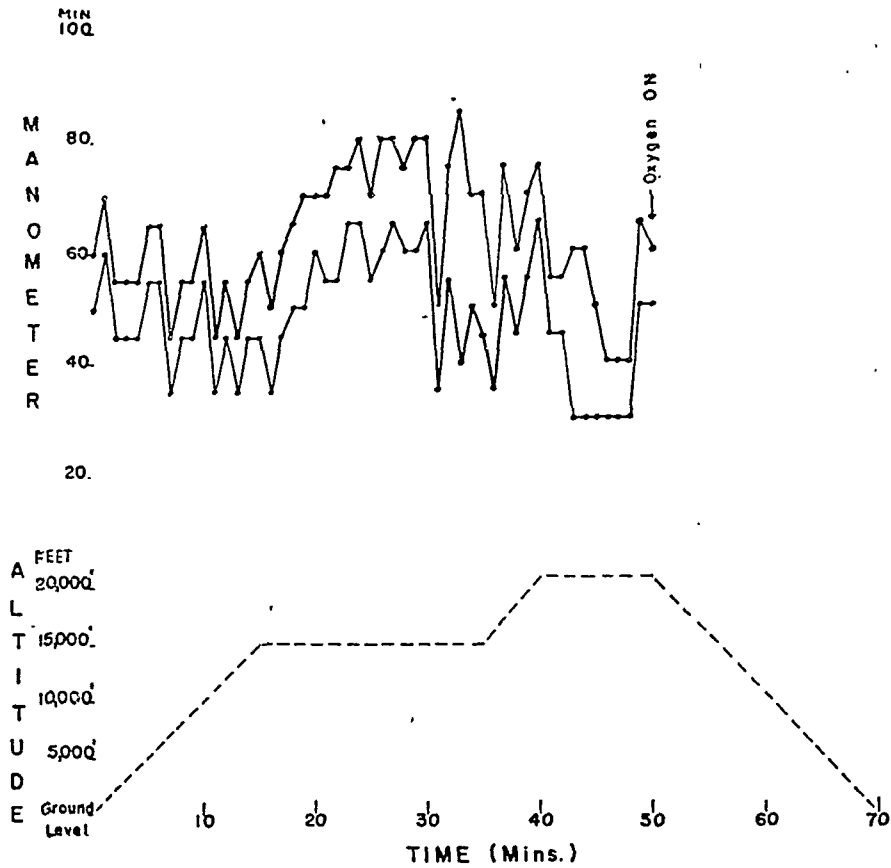
Fig. 5.—Exposure to anoxia (with patient resting and comfortable).
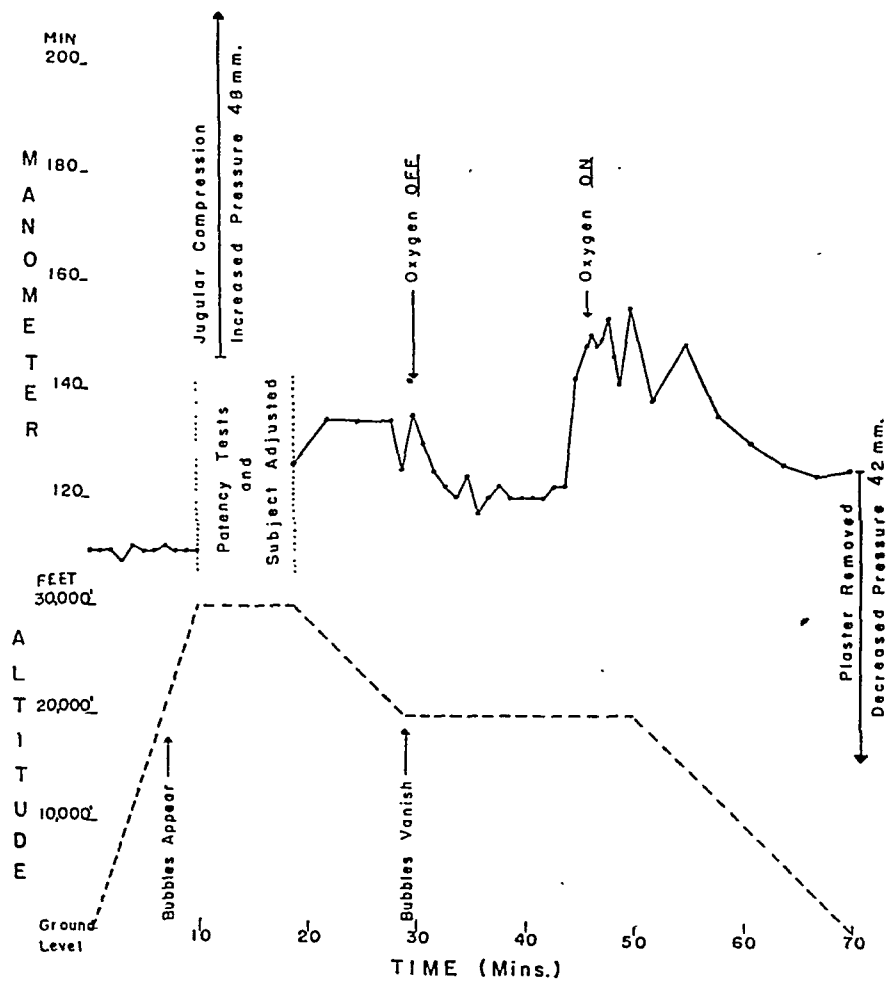
Fig. 6.—Cerebral spinal fluid pressures obtained by lumbar puncture.
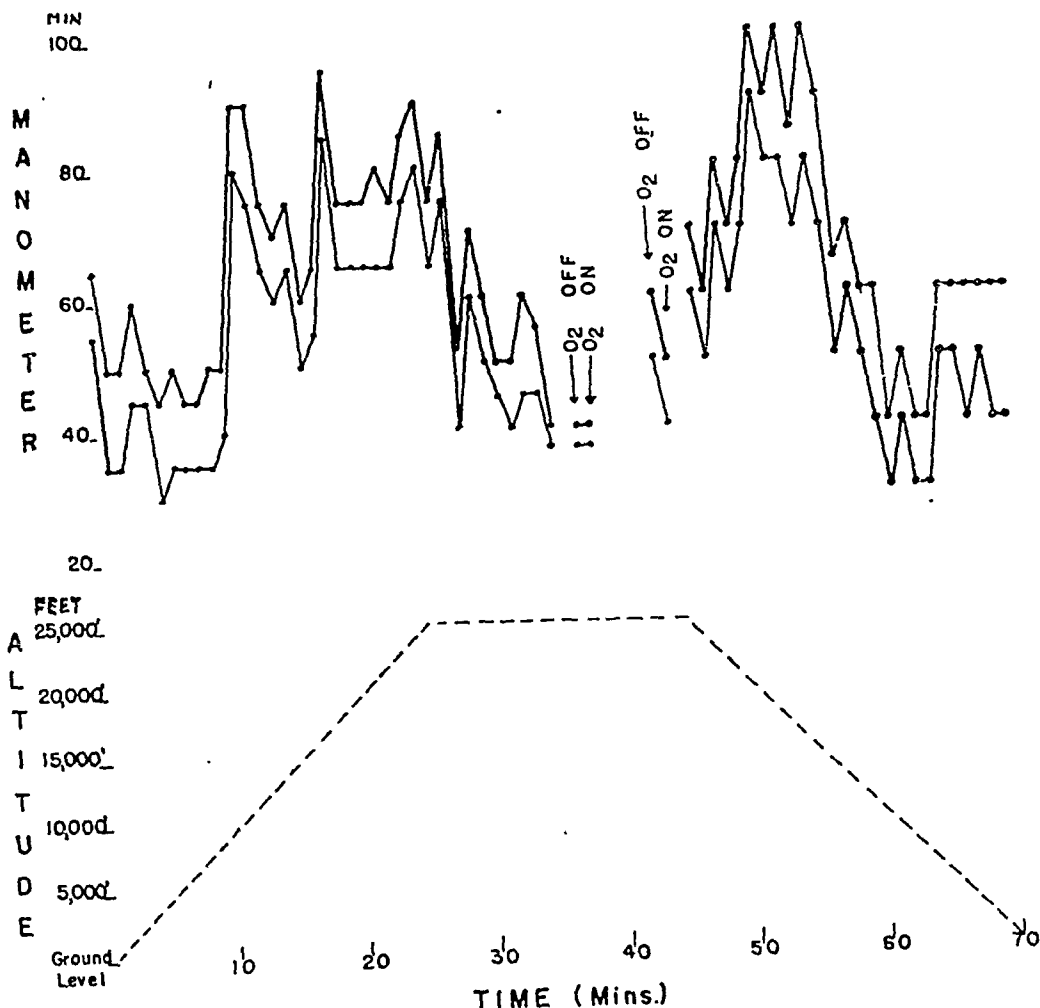
Fig. 4.—Manometric readings taken while the patient (sitting) was breathing oxygen except for two short exposures to anoxia.

two occasions, for sixty and seventy seconds respectively. Manometric readings (maximum and minimum oscillations) were taken every minute. The ascent and descent were made at the rate of 1,000 feet (604 meters) per minute.

EXPERIMENT 3: Again, with the plethysmograph in position, ascent to 15,000 feet (9,000 meters) was made without oxygen and with the subject in a comfortable reclining position. He remained at this altitude for twenty minutes, after which a further ascent to 20,000 feet (12,000 meters) was made, where he remained for ten minutes. Oxygen was then administered and descent to ground level effected. The ascent and descent were made at the rate of 1,000 feet per minute.

EXPERIMENT 4: After insertion of the lumbar puncture needle and its connection with the manometer, and while the patient was breathing oxygen, ascent was made to 30,000 feet (18,100 meters) at the rate of 3,000 feet (1,800 meters) per minute, and manometric readings were made each minute. After nine minutes at an altitude of 30,000 feet, the chamber was lowered to 20,000 feet (12,000 meters), and the oxygen mask was removed for sixteen minutes, after which it was replaced. Descent to ground level was made at the rate of 1,000 feet (604 meters) per minute. Throughout the experiment manometric readings were noted every minute except after replacement of the oxygen mask, when thirty second readings were taken. The efficiency of the manometer was checked by tests for patency (deep respiration, pressure on the jugular veins and talking).

INTERPRETATION OF RESULTS

EXPERIMENT 1.—In efficiency trials the herniometer was shown to reflect with reasonable

sensitivity any changes occurring in the intracranial pressure. Direct observations and photographic recordings (fig. 3) showed that no significant changes in intracranial pressure occurred with increased altitude (up to 30,000 feet) when the subject was breathing oxygen or was in the acutely anoxic state (exposure of two minutes and twenty seconds at an altitude of 25,000 feet).

These results are contrary to the observations of Walsh on a patient with a cranial defect of relatively minor extent at an altitude of 28,000 feet.

This experiment proves conclusively that such a subject, contrary to reports from other investigators, could safely be evacuated by air at high altitude, and even in a slightly anoxic state.

EXPERIMENT 2.—This experiment showed that no changes of intracranial pressure, other than the alterations considered as normal variations, occurred when the subject was breathing oxygen at altitudes of as high as 25,000 feet and when acute anoxia was induced at this altitude (fig. 4). These plethysmographic observations confirm the herniometric readings in the previous experiment.

RELATION OF CIRCULUS ARTERIOSUS TO HYPOTHALAMUS AND INTERNAL CAPSULE

H. S. RUBINSTEIN, M.D., Ph.D.

BALTIMORE

In studies bearing on the blood supply of the brain, a number of authors have recently stressed the contributions of the circulus arteriosus to the hypothalamus.[1] In the present study, when the branches of the circulus were traced out (fig. 1), it was observed that many of them sent terminals into the depths of the brain to supply various areas of the internal capsule (fig. 2). This communication deals with several interesting observation made in the course of this study.

My method of approach in dissection of these arteries consisted in identifying a certain vessel of the circulus, following a particular twig peripherally until it disappeared within the brain substance and then, by carefully scraping away the overlying tissue, tracing the vessel to its termination.

It was found that fixed brains were better suited for this purpose than fresh brains since the brain substance was more crumbly, and therefore more easily removed. For example, with this method the recurrent artery (fig. 3), when identified as it came off from the anterior cerebral artery, at the level of the anterior communicating artery, was traced laterally and occipitally toward the region of the insula. The overlying cortex and white matter of the temporal, frontal and parietal operculums were removed. The cortex of the insula, together with the capsula extrema, was scraped away; the external capsule was lifted up with the handle of the scalpel, and the lenticular nucleus was exposed. The branches of the recurrent artery were then followed successively into the internal capsule by gently tugging at each respective branch and scraping away the overlying nuclear substance. This method is somewhat similar to that employed by Ayer and Aitken,[2] the difference lying in the use of fixed brains in this study, rather than the fresh specimens studied by these authors.

OBSERVATIONS

The observations to be reported are graphically presented in figures 1, 2 and 3. Figure 1 shows the various branches observed and traced; figure 2, the terminations in relation to the internal capsule, and figure 3, the distribution of the recurrent arteries, which seems not to have been indicated by other authors.[3] Heubner,[3a] of course, while describing a number of the branches of the anterior cerebral artery, did not refer to any as "Heubner's recurrent artery." Lesem [3b] failed to mention this vessel at all. De Almeida [3c] referred to "Heubner's artery," which he stated may at times arise from the middle cerebral artery. Grinker [4] spoke of the "recurrent artery of Heubner," without illustrating it and cited the work of Ayer and Aitkin,[2] who likewise did not illustrate its distribution.

The accompanying figures show the distribution of these arteries.

Anterior Cerebral Artery.—The anterior cerebral artery, which supplies the more cephalic hypothalamic area through its anterior medial ganglionic branches (fig. 1), also supplies the more cephalic part of the internal capsule, i. e., the anterior limb and the genu. This it does through recurrent branches, which arise from the lateral aspect of the parent trunk.

1. Clark, W. E. L.; Beattie, J.; Riddoch, G., and Dott, N. M.: The Hypothalamus: Morphological, Functional, Clinical and Surgical Aspects, Edinburgh, Oliver & Boyd, Ltd., 1938. Finley, K. H.: Angio-Architecture of Hypothalamus and Its Peculiarities, A. Research Nerv. & Ment. Dis., Proc. (1939) **20**:286, 1940. Foley, J. M.; Kinney, T. D., and Alexander, L.: The Vascular Supply of the Hypothalamus in Man, J. Neuropath. & Exper. Neurol. **1**:265, 1942. LeBlanc, E.: Les artères de la région infundibulo-tubérienne, Trav. du Lab. de anat., Alger, 1926, pp. 14-20. LeBlanc, E.: Les artères de la fosse interpédonculaire et de l'espace perforé postérieur, ibid., 1928, pp. 16-28. Rubinstein, H. S.: The Anterior Communicating Artery in Man, J. Neuropath. & Exper. Neurol. **3**:196, 1944.

2. Ayer, J. B., and Aitken, H. F.: Note on the Arteries of the Corpus Striatum, Boston M. & S. J. **156**: 768, 1907.

3. (*a*) Heubner, O.: Die luetische Erkrankung der Hirnarterien, Leipzig, F. C. W. Vogel, 1874. (*b*) Lesem, W. W.: The Comparative Anatomy of the Anterior Cerebral Artery, Post-Grad. M. J. **20**:455, 1905. (*c*) de Almeida Prado, F.: Notes on the Anterior Cerebral Artery, Rev. de med., São Paulo **16**:75, 1932.

4. Grinker, R. R.: Neurology, Springfield, Ill., Charles C Thomas, Publisher, 1934. p. 571.

EXPERIMENT 3.—The same plethysmographic technic was employed as that used in experiment 2, but a chronic degree of anoxia was induced. Again, no changes in the intracranial pressure other than normal fluctuations were noted (fig. 5).

EXPERIMENT 4.—The creation of conditions simulating those of an intact skull was arranged by completely closing the cranial defect with a freshly poured, quick-setting plaster cast, which was firmly strapped into position. The efficiency of such an arrangement was proved by the fact than on removal of the plaster the pressure dropped 42 mm. Ascent to 30,000 feet with the patient breathing oxygen did not cause any increase in the spinal fluid pressure.

Soon after an altitude of 20,000 feet (12,000 meters) was reached, minute bubbles were noted to be rising in the manometer and lodging in the meniscus; this observation agrees with the reports of Thorner, Walsh, Boothby and Armstrong, all of whom noted bubbles, but at somewhat lower altitudes.

At 30,000 feet the patency of the manometer was tested by pressing on the jugular veins, a procedure which increased the pressure by 48 mm.; the cardiac oscillations were 1 mm. and the respiratory excursions 4 mm.

The subject was brought down to an altitude of 20,000 feet, and his oxygen mask was removed for sixteen minutes, during which time clinical anoxia of a considerable degree was induced. An increase of only 23 mm. of spinal fluid pressure was recorded toward the end of this exposure, and there was no appreciable change in the pressure on administration of oxygen (fig. 6). Although this result is inconsistent with the observations of some investigators, White and associates, working with cats, noted that in some animals anoxia produced only slight elevations of intracranial pressure, whereas in other animals the pressure remained the same. The results of this experiment further corroborate the herniographic and plethysmographic observations. Throughout all experiments the subject was exceptionally cooperative and emotionally stable.

SUMMARY

An unusual opportunity made possible a study of the intracranial pressure in a human subject at high altitudes (up to 30,000 feet) and under conditions both of sudden and of more prolonged anoxia. The methods included (1) direct observations on a huge cranial defect; (2) herniometric recordings, with photographic check; (3) plethysmographic technic, and (4) recording of the spinal fluid pressure through a lumbar puncture. In all experiments the conclusions were in agreement: There is no significant increase in the intracranial pressure in man (other than normal variations) at high altitude and under conditions either of sudden or of more prolonged anoxia.

These results are regarded as of particular importance with respect to transportation of casualties and sick persons by air. Moreover, experience with other patients with head injuries indicates that these casualties tolerate air transportation well. In fact, it may be to them a life-saving measure by providing rapid, definitive treatment. Any specific contraindication bearing on changes in intracranial pressure is not in accord with the experimental and practical evidence obtained from the case just described.

Montreal Neurological Institute.

Recurrent Artery.—At its origin from the internal carotid artery, the anterior cerebral artery (fig. 1) gives off numerous fine, penetrating branches. These branches, together with similar twigs from the anterior communicating artery, are soon lost in the supraoptic area. In the region of the anterior communicating artery, the anterior cerebral artery gives off its recurrent branch, which passes laterally and divides into several twigs (fig. 3). One of these twigs passes to the region of the external capsule; another twig passes into the anterolateral aspect of the lentiform nucleus and continues medially into the head of the caudate nucleus and the anterior limb of the internal capsule. *Another twig passes through the cephalic part* of the lenticular nucleus caudal to the former branch and can likewise be traced to the anterior limb of the internal capsule. Two or three small branches then penetrate the midregion of the lateral protuberance of the lentiform nucleus and continue to the genu of the internal capsule. One of the more occipital of these twigs may also extend into the more frontal part (arm area) of the posterior limb of the internal capsule.

Accessory Recurrent Artery.—When this vessel is present, it may be given off from the lateral aspect of the anterior cerebral artery approximately midway between its origin and its anterior communicating branch. When present, the accessory recurrent artery sends branches which may parallel in distribution the branches of the recurrent artery. The accessory recurrent artery is not constant. As a matter of fact, the recurrent artery, too, may be absent bilaterally. In still other brains it may be present on one side and absent on the other. Twigs from the middle cerebral artery then supply the areas previously described as being nurtured by the recurrent arteries.

Middle Cerebral Artery.—The middle cerebral artery, some of the anterior lateral ganglionic twigs of which reach the more lateral hypothalamic areas, sends well marked branches to the anterior limb, the genu and the anterior two thirds of the posterior limb of the internal capsule.

Posterior Communicating Artery.—This artery, the hypothalamic branches of which supply the lateral tuberal and lateral mamillary areas, also sends twigs to the genu of the internal capsule.

Internal Carotid Artery.—The internal carotid artery, which sends small, medially disposed branches (unlabeled in figure 1) to the optic chiasm, the infundibulum and the tuberal area, also sends a prominent occipitolaterally coursing branch, the anterior choroidal artery, to supply the genu, the posterior limb and the retrolenticular component of the internal capsule.

Posterior Cerebral Artery.—This artery, which sends branches to the mamillary bodies, also gives off posterior lateral ganglionic branches, which supply the posterior limb and the retrolenticular and sublenticular components of the internal capsule.

COMMENT

From these observations it may be seen that practically all parts of the internal capsule have a multiple blood supply, since even the sublenticular contingent may receive additional twigs (other than those shown in figure 2) from the posterior choroidal branches of the posterior cerebral artery (fig. 1) or from penetrating branches of the superior cerebellar artery as this vessel winds around the cerebral peduncle.

The recurrent branch of the anterior cerebral artery (Heubner's artery) has been observed as a single vessel in many brains, but more often than not additional branches, which could be logically referred to as accessory recurrent branches, have been observed (fig. 1). These accessory recurrent arteries reenforce the recurrent arteries (of Heubner).

While most of the segments of the circulus arteriosus supplying the hypothalamus send branches to the internal capsule, it is interesting that the anterior communicating artery fails to do so. Perhaps this is because the twigs of this artery, when present, are strictly midline structures while the internal capsules are more laterally disposed.

The disposition of these vessels in relation to the hypothalamus and the internal capsule is important from several standpoints. First, it shows that in spite of the dramatic, and in most instances tragic, cessation of function following gross cerebrovascular accidents, for the greater part of the patient's life prior to such an overwhelming upset nature has been bountiful in the multiple blood supply to many important nerve centers. This is true not only for the internal capsule but for the greater part of the hypothalamus.

Furthermore, a knowledge of this disposition helps in the understanding, and therefore in the prognosis, of vascular accidents observed clinically. For example, it is now known that occlusion of the recurrent branches of the anterior cerebral artery results in damage to the cephalic portion of the caudate and lenticular nuclei and to the intervening internal capsule. This results in facial and lingual paralysis (defect in the internal capsule) and rigidity (involvement of
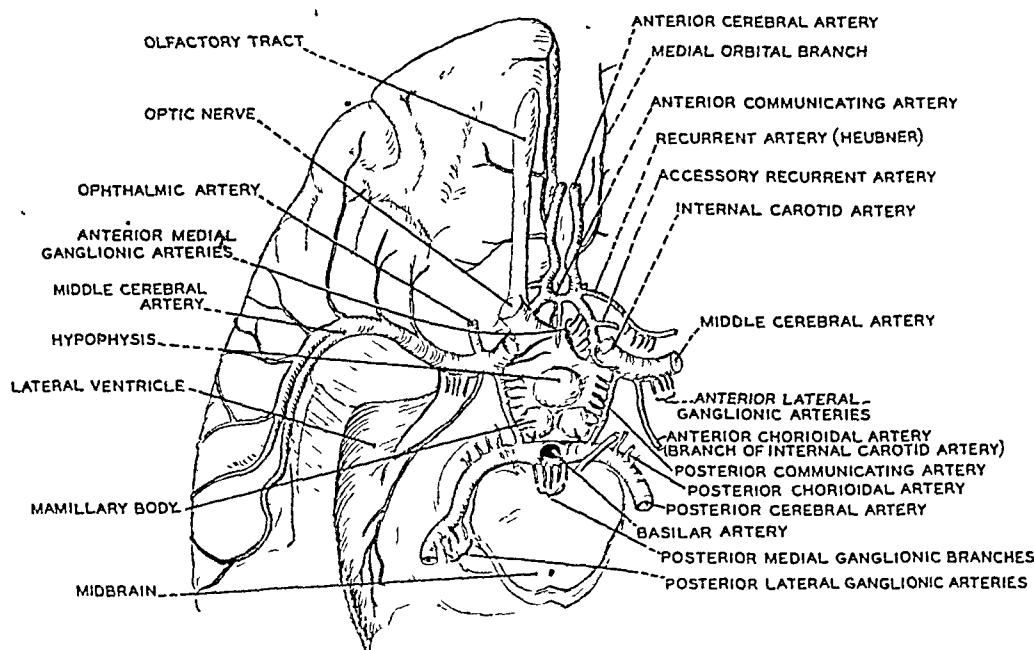
Fig. 1.—The arterial circle with its branches to the basal ganglia and the hypothalamus. Tuberal branches (not labeled) are given off from the right internal carotid artery.
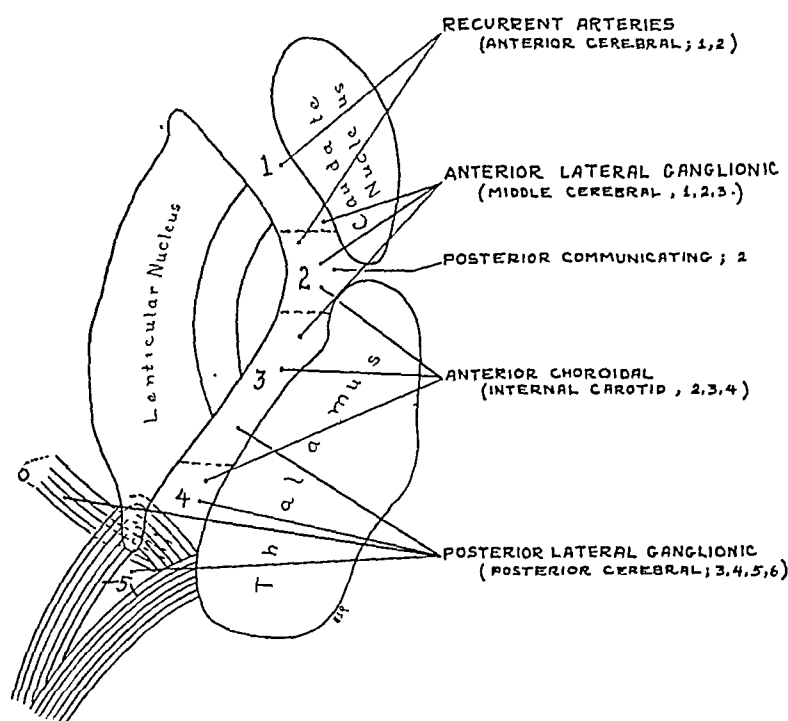
Fig. 2.—Diagram showing blood supply to various components of the internal capsule. Leaders and numbers indicate the parts supplied by the arteries (parent stems in parentheses).

The components of the internal capsule are designated as follows: *1* indicates the anterior limb (associative in function); *2*, the genu (motor fibers to the face); *3*, the anterior two thirds of the posterior limb (motor); *4*, the posterior third of the posterior limb (sensory); *5*, retrolenticular component (visual), and *6*, sublenticular component (auditory).
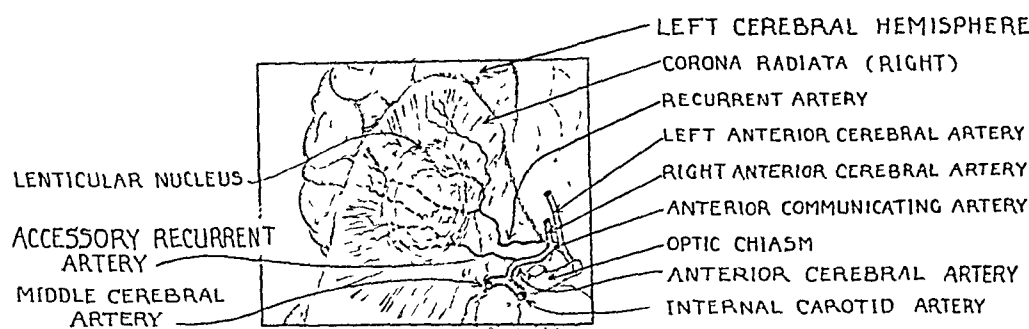
Fig. 3.—Dissection showing the recurrent and accessory recurrent arteries. The broken line branches indicate their penetration through the substance of the lenticular nucleus in order to reach the internal capsule.

The area of richest blood supply is the genu of the internal capsule.

Study of the recurrent branches of the anterior cerebral artery revealed that, in addition to the recurrent branch of Heubner, accessory recurrent arteries exist. These vessels, when present, parallel the distribution of the recurrent artery. [Correlations have been presented between the pathological involvement of the recurrent and anterior choroidal arteries and the respective clinical findings. In addition, discrepancies between injection experiments and dissectional methods of study have been considered and an attempt has been made to reconcile these differences.]

Concomitant vasomotor and visceral phenomena observed in cases of otherwise grossly somatic clinical defects incident to cerebrovascular accidents are explained on the basis of coincident ischemia of the hypothalamus.

2349 Eutaw Place.

the basal ganglia). Yet only by appreciating the quadruple blood supply to the genu of the internal capsule through the additional anterior lateral ganglionic branches (middle cerebral artery), the posterior communicating artery and the anterior choroidal branch of the internal carotid artery can one understand why the facial paralysis in most instances clears up while the rigidity persists.

While in most cases of hemiplegia purely motor disturbances result from damage to the anterior lateral ganglionic branches of the middle cerebral artery, one not infrequently sees a hemiplegic patient with sensory disturbances corresponding to the motor deficits. Only recently a colleague asked how such a clinical picture could be explained. Figure 2 makes it clear that a lesion involving the anterior choroidal artery may lead to just such a result.

Finally, it is helpful to remember the common source of the blood supply to the hypothalamus and to the internal capsule when one seeks an explanation of various visceral manifestations observed in cases of otherwise somatic defects. Ischemic changes have frequently been observed in the hypothalamus of patients with vascular accidents in other areas of the brain. Such changes not only may contribute to the vasomotor phenomena which affect the hemiplegic patient but may account for the hitherto inexplicable glycosuria and hyperproteinemia observed in some patients with acute cerebrovascular accidents.

The observations here reported are at variance in certain respects with those of Alexander.[5] This author, in his beautiful injection experiments, reported that the various areas of the basal ganglia and the internal capsule were completely dependent on specific and respectively single vascular sources. To the anterior limb and the dorsal part of the posterior limb of the internal capsule Alexander ascribed the striate arterioles; to the genu, the capsular branches of the internal carotid artery, and to the ventral part of the posterior limb and the retrolenticular component, the anterior choroidal artery. In this scheme, this author and I are in greatest agreement with respect to the anterior limb, since he derived his "striate arterioles" from both the anterior and the middle cerebral artery. The greatest difference relates to the genu to which area I have traced branches of the anterior cerebral artery, the middle cerebral artery, the posterior communicating artery (when present)

5. Alexander, L.: The Vascular Supply of the Strio-Pallidum, A. Research Nerv. & Ment. Dis., Proc. (1940) 21:77, 1942.

and the anterior choroidal artery. It is difficult to reconcile such differences, especially since, even grossly, more than one vessel can often be traced into a particular zone of the internal capsule, unless one assumes either that Alexander's injections fell just short of sufficient pressure or that not all the vessels of a particular group were included in what was later taken to be a group injection.

The latter assumption is particularly engaging, since it is supported by a study of Alexander's figure 26. In this figure, the recurrent arteries are distinctly shown coming off (on either side of the brain) from the lateral aspect of the respective anterior cerebral artery at the level of the anterior communicating artery (unlabeled in his figure). These twigs and the accessory recurrent branches, when present, can usually be traced to the region of the anterior limb and the genu of the internal capsule.

In his injections of the striate branches, Alexander consistently tied off the anterior cerebral arteries near their origins, thereby excluding the recurrent arteries. One would assume therefore that he considered these branches foreign to the medial ganglionic vascular group (his "striate branches of the anterior cerebral artery"). Yet when Dr. James W. Ayer raised the question of anomalous branches to this region of the basal ganglia and referred specifically to the description of Heubner [5] (page 128), Alexander, in his response (page 130), admitted certain "minor variations" with reference to his figure 26. However, instead of identifying the unlabeled branches in this figure as recurrent arteries, he referred to them as components of the striate branches of the anterior cerebral artery (". . . entering striate arteries are derived from two large mainsprings originating from the anterior cerebral artery"). If Alexander meant to include these recurrent branches as part of the medial ganglionic vascular system, as he did in his response to Dr. Ayer, they should have been injected, together with the other twigs of this group. If, on the other hand, as one may judge from his excluding them from injection, he considered that these recurrent branches did not belong to the medial ganglionic group, they should have received independent attention.

SUMMARY AND CONCLUSIONS

In a study of the relation of the circulus arteriosus to the hypothalamus and the internal capsule, it was observed that in many instances a common parent stem supplies the hypothalamus and the internal capsule. All parts of the internal capsule are supplied by more than one source.

supplementary vitamins and sulfadiazine, was instituted.

On August 11 spinal puncture at the third or fourth lumbar level yielded no fluid, but at the second lumbar level the initial pressure was 230 mm. of water. Twenty-five cubic centimeters of clear, colorless fluid was removed, and the final pressure was 130 mm. of water. No block was noted. At the fifth lumbar level the initial pressure was 130 mm. of water. The fluid was bloody, and there was evidence of partial block. A specimen of spinal fluid from the latter level contained 50 mg. of total protein and 37.5 mg. of sugar per hundred cubic centimeters and 7 lymphocytes and 11 polymorphonuclear leukocytes per cubic millimeter. No organisms were noted in smears or on culture of the fluid.

On October 15 a myelogram obtained with pantopaque [1] showed evidence of diffuse lumbar arachnoiditis (figure, 1). Excision of the laminas from, the second to the fifth lumbar vertebrae inclusive was performed

this period occasionally showed evidence of cystitis, with 20 to 30 polymorphonuclear leukocytes per high power field. Nonhemolytic staphylococci and Escherichia coli were noted in smears and on cultures. Lumbosacral pain and muscle spasm continued, however, and roentgenographic examination on December 26 showed a destructive process involving both surfaces of the bodies of the second, third and fourth lumbar vertebrae, the inferior surface of the fifth lumbar vertebra and the superior surface of the first sacral vertebra (figure, 2). The process was most pronounced at the second and third lumbar vertebrae, with sclerosis around a cup-shaped area of dissolution in the centrum. There was slight narrowing of the second lumbar intervertebral space. Examination on Feb. 1 and Feb. 12, 1944 revealed a decreased reaction of the vertebral bodies surrounding the previously described areas of osteomyelitic destruction. Surgical
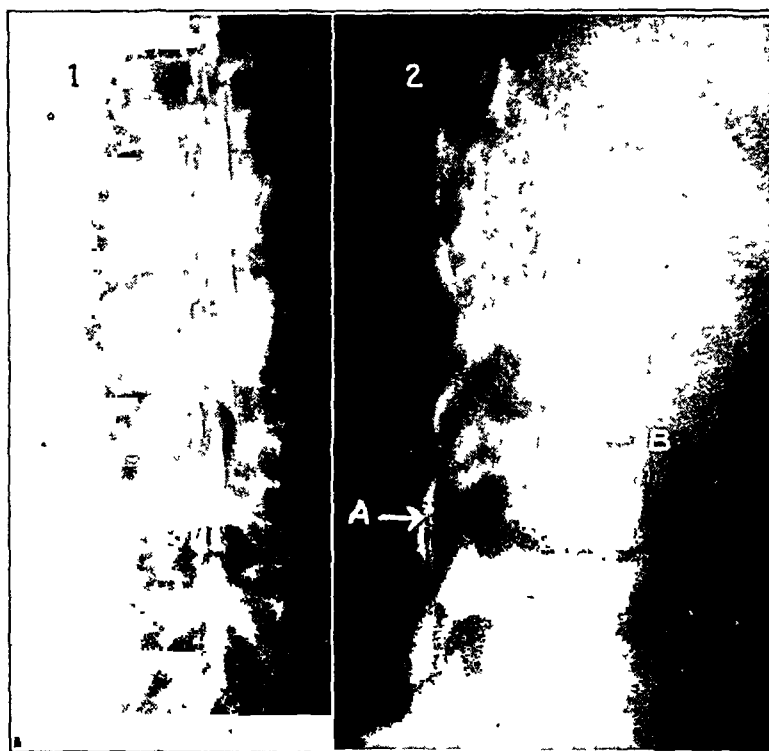
1, myelogram obtained with pantopaque, showing chronic arachnoiditis; *2,* myelogram, showing (*A*) tantalum foil, inserted at operation, and (*B*) osteomyelitic involvement of the body of the third lumbar vertebra.

on October 21. The arachnoid was firmly attached to the dura and the adjacent roots of the cauda equina. In the exposed area, the nerves were so solidly adherent that no fluid was seen, the cauda equina resembling a virtually solid column. Spinal fluid was not obtained until the level of the first lumbar vertebra was reached. A section of tantalum foil was placed over the exposed roots after they had been carefully separated, and the dura was not closed.

After operation the paresthesias and sensory changes disappeared. There was areflexia over the lower extremities, with hyperactive reflexes and a positive Hoffmann sign over the upper extremities. Retention of urine necessitated frequent catheterization, resulting ultimately in an automatic bladder. The urine during

treatment was not advised because of the slow, but definite, advancement, and active physical therapy was instituted. Penicillin was not given, owing to failure to obtain any organism on culture. Flexion contracture of the hip, knee and achilles tendon developed on both sides, necessitating application of casts, with frequent blocking. The patient continued to show gradual improvement, and on her last examination, on August 30, there were only slight evidence of previous contractures and moderate intermittent pain in the lower part of the back. The neurologic status was otherwise unchanged. Roentgenograms showed the presence of healing about the previous areas of involvement.

The cause of the massive adhesive arachnoiditis in this case has not been determined, but it is probable that the anesthetic was introduced into the subarachnoid space. Whether the process was a sequel of the anesthesia itself and the resultant reaction, either toxic or chemical, or whether a latent organism or virus was activated or introduced at the time of injection of the anesthetic, with production of a low grade infection,

1. Pantopaque (a mixture of ethyl esters of isomeric iodophenylundecyclic acids, containing 30.5 per cent of iodine in the form of organic combinations) is a new radiopaque oil that is thinner and less viscous than the older iodized oils. It has a specific gravity of 1.263 at 20 C.

NEUROLOGIC COMPLICATIONS FOLLOWING THE USE OF CONTINUOUS CAUDAL ANESTHESIA

CAPTAIN WILLIAM G. PEACHER AND MAJOR ROBERT C. L. ROBERTSON

MEDICAL CORPS, ARMY OF THE UNITED STATES

Numerous investigators have previously demonstrated the value of caudal anesthesia in obstetrics, and the method has been recently modified and popularized by Hingson and Edwards and others. All have agreed that its use should be restricted to the specialist in adequately equipped hospital centers because of the possibility of serious complications. Continued study only will determine its ultimate value for more general use. We have recently had the opportunity of studying 2 cases with complications which have not as yet been encountered in the literature.

REPORT OF CASES

CASE 1.—A woman aged 26 had low forceps delivery of a normal living male infant, with repair of a left lateral episiotomy incision on Oct. 17, 1942. Caudal anesthesia was induced by the ureteral catheter technic, and 960 cc. of a 1.5 per cent solution of procaine hydrochloride was administered, at the rate of 20 cc. per hour. Delivery was slightly prolonged but uneventful. Localized pain over the lumbosacral region with bilateral sciatic radiation was noted shortly after parturition. There was also urinary retention, necessitating catheterization for a few days. There were analgesia in the right saddle area and hypesthesia to the level of the second lumbar segment on the right side and to the level of the fourth lumbar segment on the left side. The patient had pain on raising the straight leg, and the Lasègue 'sign was positive bilaterally at a flexion of 20 degrees. The reflexes were active and equal on the two sides. ·

Cystoscopic and retrograde pyelographic studies, on October 21, showed no calculi or evidence of pathologic process except for elongation of the ureters, with more pronounced distention of the left ureter than of the right. The roentgenographic evidence was consistent with the existence of a recent pregnancy.

On October 25 culture of fluid aspirated from the sacral portion of the spinal canal showed that the predominating organism was a hemolytic streptococcus. Staphylococcus albus was also occasionally noted. On October 26, 2 to 3 drops of thick, purulent material was aspirated from the spinal canal at the fourth lumbar level. Prior to removal of the fluid resistance had been encountered, but whether from the ligamentum flavum or from the dura one could not be certain. The specimen, therefore, may have been from either the subdural or the epidural space. No spinal fluid was obtained during this procedure. A smear revealed numerous leukocytes and a few gram-positive diplococci. Culture yielded pure Staph. albus haemolyticus. The rest of the laboratory studies gave essentially negative results. There were slight daily elevations in temperature, to

100 or 101 F., with a corresponding rise in the pulse rate to 90 or 100 a minute. No change in the respiratory rate or the blood pressure was noted. Under routine sulfathiazole therapy, 15 grains (0.975 Gm.) every four hours for two weeks, the patient showed rapid improvement. She was asymptomatic and neurologically normal both on her discharge from the hospital, on November 10, twenty-four days post partum, and on her most recent follow-up examination, on March 11, 1944.

CASE 2.—A woman aged 22 was delivered of a normal, viable female infant, with repair of a left mediolateral episiotomy incision, on June 17, 1943. Caudal anesthesia was induced by the ureteral catheter technic, and 335 cc. of a 1.5 per cent solution of metycaine hydrochloride was given, at the rate of 20 cc. per hour. The delivery and postpartum course were uneventful, and the patient was discharged, without symptoms, on June 24. Pain in the lower part of the back with bilateral sciatic radiation, first noted on June 26, necessitated readmission on July 1. A questionable sensory level was noted at the third lumbar segment on both sides; reflexes over the lower extremities were hyperactive but equal on the two sides, and the Kernig and Brudzinski signs were present. Drainage of the urinary bladder was necessary for two weeks because of retention. The symptoms were thought to be due to epidural cellulitis, rather than to abscess. The temperature and pulse rate showed daily elevations, averaging 103 F. and 120 per minute respectively. The blood pressure and the respiratory rate presented no deviations from normal. There were accompanying leukocytosis, with a count of 10,000 white cells, and anemia, with a red cell count of 3,500,000 and a hemoglobin concentration of 75 per cent. All symptoms gradually disappeared after institution of sulfadiazine therapy, 15 grains being given every four hours for four weeks. The patient was discharged as improved on July 24.

Because of continued pain and spasm over the lumbar region and the lower extremities and the development of generalized paresthesias, the patient was again admitted on August 5. There was evidence of widespread involvement of the spinal cord. The reflexes were hyperactive throughout, and the Kernig and Brudzinski signs were elicited. Slight nuchal rigidity was noted. The Babinski, Chaddock, Oppenheim and Hoffmann signs were present bilaterally, with transient patellar and ankle clonus on the left side. There was generalized muscular atrophy, which was greater in the lower extremities. The most pronounced deviations noted in a study of the blood were leukocytosis, with a white cell count of 14,800, and anemia, with a red cell count of 3,250,000 and a hemoglobin concentration of 70 per cent. The temperature, again, showed slight daily elevations to 100 or 101 F., but little change in the pulse and respiratory rates or in the blood pressure was seen. Intensive supportive therapy, including a diet of high caloric and vitamin content, administration of liver, frequent transfusions and administration of

Case Reports

MENINGIOMA OF THE VELUM INTERPOSITUM

HENRY T. WYCIS, M.D., PHILADELPHIA

Cushing divided meningiomas of the tela choroidea superior (velum interpositum) into two groups, lateral and posterior tumors of the velum. Posterior tumors of the velum are indeed rare. In a review of the literature reports of but 4 such tumors were found. Horrax,[1] in 1936, resected the occipital lobe and removed successfully a meningioma, weighing 40 Gm., overlying the quadrigeminal region. The tumor was of fibroblastic type, with no psammoma bodies. Araki[2] had experience with 2 meningiomas in this location. Both tumors were successfully attacked by splitting the splenium of the corpus callosum and removing the growth piecemeal. One of these tumors had psammoma bodies and was visible roentgenographically. The tumor reported by Balado and Tiscornia[3] was a meningioma arising from the free posterior margin of the falx cerebri. Suboccipital exploration in two stages for an associated medulloblastoma in the midline of the vermis terminated fatally.

The following case is that of a psammomatous meningioma of the posterior portion of the velum interpositum. The tumor was approached by a combined suboccipital and occipital craniectomy, with section of the tentorium.

REPORT OF A CASE

History.—Miss C. H., aged 13, was admitted to Dr. S. F. Gilpin's neurologic service at Temple University Hospital on Jan. 3, 1944, having been referred by Dr. Alexander Silverstein, of Philadelphia.

Except for a reported attack of rheumatic fever four years before, she had apparently been well until six months prior to admission, when headaches appeared in the right temporal region. The attacks lasted approximately two hours and could be relieved by medication. A history of definite disturbance in gait could not be obtained, but the mother stated that walking had always been somewhat irregular. The left pupil had been larger than the right since birth. One week before admission the patient noted sudden onset of numbness of the left side of the face, which progressed downward to involve the whole left side of the body.

1. Horrax, G., cited by Cushing, H., and Eisenhardt, L.: Meningiomas, Springfield, Ill., Charles C Thomas, Publisher, 1938.

2. Araki, C.: Meningioma in the Pineal Region: A Report of Two Cases Removed by Operation, Arch. f. jap. Chir. **14**:1181-1192, 1937.

3. Balado, M., and Tiscornia, A.: Tumor de la hoz del cerebro pediculado a desarrollo subtentorial, Arch. argent. de neurol. **1**:297-310, 1927.

The entire episode was of fifteen minutes' duration. At this time a physician noted increase in headache, vomiting, somnolence, inability to concentrate and unsteadiness of gait. During the week prior to hospitalization there were frequent attacks of fainting, with respiratory distress. She was accordingly referred to the neurologic service for observation.

Examination.—The patient was well nourished and cooperative. General physical examination revealed nothing significant. Neurologic examination revealed the following signs: There was a "cracked pot" sound on percussion of the skull, indicating increased intracranial pressure. The gait showed mild ataxia, with swaying to the left side. Both pupils were dilated, but the left one was larger than the right. The pupils did not respond to light but reacted to accommodation. The fundi revealed bilateral papilledema of 2 D. A relative central scotoma was present in the left eye. The extraocular movements appeared full in all directions except for partial weakness of upward gaze. On the patient's looking downward, there was a rotatory nystagmus in the clockwise direction. On her looking to the right, there was horizontal nystagmus to the right with a clockwise rotatory component. On her looking to the left, there was left horizontal nystagmus with a rotatory clockwise component. The corneal reflexes were active and equal on the two sides. No sensory or motor disturbances were noted in any of the trigeminal fields. The expressional movements of the face were normal. The audiometric readings showed partial conduction deafness in the right ear. There was no hoarseness or dysphagia. The ninth, tenth, eleventh and twelfth cranial nerves did not appear to be involved.

The deep tendon reflexes were notably decreased, but the Babinski sign could easily be elicted bilaterally. The Hoffmann sign could not be obtained. Sensory disturbances were not noted in any of the cutaneous dermatomes.

There was striking generalized hypotonia, with mild dysmetria and adiadokokinesia, on the left side. Tension of the muscles of the neck was increased, however. When the arms were raised above the head, the left forearm flexed at the elbow, and the hand deviated laterad. The entire left extremity deviated away from the midline.

The laboratory studies, including serologic tests, gave normal results.

Roentgenograms of the skull showed a dense calcification, about the size of a pigeon egg, in the midline, just inferior to the usual position of the pineal body (fig. 1). There were other signs of increased intracranial pressure, such as widening of the suture lines, erosion of the dorsum sellae and a silver-beaten appearance of the inner table of the skull.

The patient was transferred to Dr. M. Scott's neurosurgical service for operation.

Operation (January 2).—Suboccipital craniectomy, combined with occipital craniectomy and tentorial section was carried out.

The patient was placed in the cerebellar position. A flap was constructed on the right side, the vertical limit of which extended from the spinous process of the

has not been determined. The presence of intermittent slight elevations in temperature was evidence of the latter. Finally, the extent of the arachnoiditis has not been determined but must be maximal in the lumbo-sacral region. It is hoped that separation of the roots of the cauda equina will reestablish circulation of the spinal fluid and result in ultimate recovery. The osteomyelitis might be attributed either to hematogenous spread or to direct extension.

COMMENT·

Hingson and Edwards [2] recently analyzed critically the collected results in the first 10,000 cases in which continuous caudal anesthesia was used. They reviewed the entire subject, but we are concerned only with the neurologic sequelae, the incidence of which constitutes 2.2 per cent of all complications recorded.

Occasional need for catheterization is not uncommon, and only 1 case was mentioned in which there was urinary retention of three weeks' duration. The authors state the opinion that injection of metycaine in distilled water may produce neuritis as a result of contact of the nerve trunks with the products of hemolysis of the red cells. Use of the lateral recumbent position prior to delivery has largely obviated the early high incidence of pain in the lower part of the back. The convulsions present in 2 of the authors' cases were due to accidental intravascular injection and an overdosage of the anesthetic. Both patients recovered. Headaches were transient and were attributed to too rapid a rate of injection. In 2 cases there was subjective numbness—in 1 case with a level at the fifth cervical segment, which cleared in three weeks, and in the other with sensory impairment in the vaginal vault and the perineum, which had continued until the time of the report, for three months. In 1 case a transient hysterical reaction developed during anesthesia. Vertigo, tinnitus and visual changes were also mentioned.

The incidence of severe cellulitis or peridural abscess was 0.05 per cent. A staphylococcic infection of the extradural space at the fifth lumbar and the first sacral levels, with bacteremia, was responsible for death, thirty-one days post partum, in 1 case. In the remaining cases the patients responded to treatment with sulfonamide compounds. In the routine therapy of this complication the authors suggested aspiration of purulent exudate from the caudal part of the canal and instillation of 75,000 units of penicillin in 40 cc. of isotonic solution of sodium chloride, to be repeated at least once two hours later. If incision and drainage are necessary, irrigation with a 5·per·cent solution of sulfathiazole is recommended every hour for twelve hours. The oral use of the sulfonamide compounds is maintained when the patient is resistant to penicillin and when the latter drug is not available.

An additional complication recorded by Manalan [3] is the development of staphylococcic meningitis on the third postpartum day. This sequela was attributed to the employment of caudal anesthesia, although aspiration of the contents of the sacral portion of the canal gave no evidence of infection. Recovery was complete. Bishop [4] mentioned drowsiness, vomiting, pyrexia, a rise in the level of anesthesia and paresis of the right side of the face and the right arm after the use of metycaine. Subdural injection probably resulted, and the patient's weakness gradually disappeared after her discharge from the hospital.

SUMMARY

We have presented 2 obstetric cases with unusual complications following the use of continuous caudal anesthesia. In 1 case the sequela was either an epidural or a subdural abscess, which responded to treatment with a sulfonamide compound with complete recovery. The exact location of the abscess was not determined, as no operation was performed. This case was previously briefly reported by Siever and Mousel [5] as that of epidural abscess. The other complication was arachnoiditis involving the cauda equina with secondary osteomyelitis, the final outcome of which is still in doubt because of a residual pathologic process. It appears, therefore, that the role of infection in the production of complications following the use of caudal anesthesia is second only to the introduction of the anesthetic into the subarachoid space, and this view has also been recently expressed by Gready.[6]

2. Hingson, R. A., and Edwards, W. B.: Continuous Caudal Anesthesia, J. A. M. A. 123:538 (Oct. 30) 1943.

3. Manalan, S. A.: Caudal Block Anesthesia in Obstetrics, J. Indiana M. A. 35:564 (Oct.) 1942.

4. Bishop, H. F.: Continuous Caudal Anesthesia, S. Clin. North America 23:1565 (Dec.) 1943.

5. Siever, J. M., and Mousel, L. H.: Continuous Caudal Anesthesia in Three Hundred Unselected Obstetric Cases, J. A. M. A. 122:424 (June 12) 1943.

6. Gready, T. G.: Some Complications of Caudal Anesthesia and Their Management, J. A. M. A. 123:671 (Nov. 13) 1943.

right pupil was dilated, and the left pupil was unchanged. There was no response to light. The dressing was wet with the fluid from the draining intraventricular cannula.

Fifth Day: Respiration was so labored and obstructed that bronchoscopic aspiration had to be done on several occasions to clear the upper tracheal passages of crusts and mucopurulent exudate. A tracheotomy was performed by Dr. Charles Norris, with immediate improvement in the patient's condition.

Next Nine Days: The patient had recurrences of respiratory difficulty, with periods of apnea and Cheyne-Stokes respiration. Several times respiration ceased and had to be restored by artificial means. At these times the operative flap became full and bulging, and *ventricular puncture offered only temporary relief.* At other times the tracheotomy tube became filled with crusts, requiring changing of the tube, and even repeated bedside bronchoscopic aspirations which were done by Dr. Charles Norris.

Sterile methylrosaniline chloride, introduced into the ventricular system, could not be recovered from the spinal fluid below the level of injection. This indicated a block, probably in the region of the aqueduct of Sylvius.

January 21: Jacksonian seizures were seen to involve the arm, face and leg on the right side. That evening, because of increased respiratory difficulty, a second exploration was decided on. Dr. Michael Scott suggested that the Torkildsen procedure might be used with benefit.

Reexploration.—The former craniotomy flap was elevated. The right cerebellar hemisphere was noted to be twice its size, swollen and tense, and the tonsil on the right side had herniated through the lower dural opening. The foramen magnum on the patient's left side was further decompressed. The dural constriction was cut. It was almost impossible to view the former operative site.

After intravenous administration of 20 cc. of 20 per cent sodium chloride, edema subsided and more room was available. The tonsils of the cerebellum were separated, and a ureteral catheter was inserted along the floor of the fourth ventricle, through the aqueduct of Sylvius and into the third ventricle. The course of the catheter was verified by passing air into the catheter below and observing its escape from the cannula in the ventricle above, which indicated a release of the block.

A second, no. 14 French, catheter, was inserted into the lateral ventricle in place of the cannula and passed around the cerebellum to the foramen magnum below; thus a ventriculostomy was done. The dura was allowed to remain open. The fascial layers were closed with silk as usual; the skin was closed with silk, and only the ureteral catheter was drawn out through the incision.

The most gratifying result was the immediate abeyance of the Cheyne-Stokes respiration. Breathing, although rapid, was regular. The color was good, and the condition was improved.

Postoperative Course.—On the two following days Cheyne-Stokes respiration did not recur, but breathing became more rapid and shallow. The spinal fluid pressure was 10 mm. of mercury, but there was still xanthochromia. The tracheotomy tube functioned satisfactorily. Both pupils were dilated, with no response to light. The corneal reflex was not obtained. The left eyeball was turned downward and outward.

Nineteen days after the original operation, or nine days after the second exploration, a sudden hemorrhage

occurred from the tracheotomy tube, resulting in sudden asphyxia and death.

A roentgenogram of the skull was taken post mortem to verify the position of the catheters, as well as to ascertain the amount of the tumor removed (fig. 2). No evidence of the calcification seen in the tumor on the original films could be found. The ureteral catheter was observed to pass from the fourth ventricle through the aqueduct of Sylvius into the third ventricle. The large catheter from the right lateral ventricle to the foramen magnum (ventriculostomy) was in its proper position.

Histologic Character of Tumor.—The pathologic specimen measured 4 cm. in its greatest diameter. The meningeal surface was glistening but notably injected. The underlying portion had a grayish white, granular appearance, and palpation imparted a gritty sensation. Microscopic examination revealed a loose, vascular, edematous stroma, interspersed with numerous ovoid spindle cells. At times the spindle cells displayed a tendency to arrange themselves in bundles. Scattered profusely throughout the tumor were numerous psammoma bodies. The diagnosis was meningioma.

Postmortem Examination.—There was pronounced internal hydrocephalus. No evidence of residual tumor tissue was to be seen. Inspection of all the great
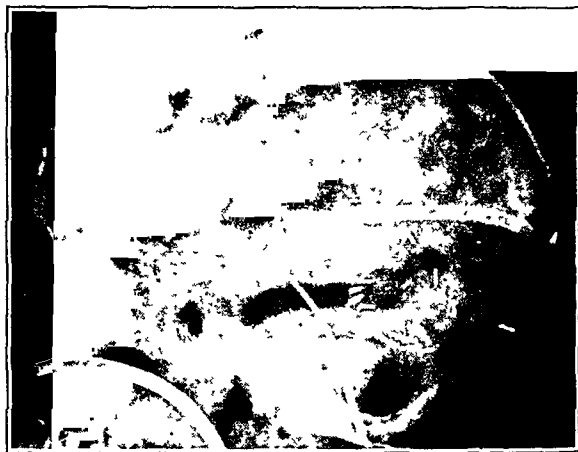
Fig. 2.—Roentgenogram of the skull, taken post mortem, showing passage of the ureteral catheter along the floor of the fourth ventricle through the aqueduct of Sylvius. A partial ventriculogram was obtained by injection of air into the ureteral catheter at its exit. The larger rubber catheter is seen to pass from the lateral ventricle around the cerebellum, beneath the skin, to the foramen magnum area below. Note the absence of the calcified tumor shown in figure 1. The centrally placed clips mark the position of removal of the tumor.

venous sinuses, including the vena cerebri magna and the internal cerebral veins, failed to show any evidence of thrombosis. The ureteral and the no. 14 French rubber catheter were noted to be in the positions shown in the roentgenogram.

COMMENT

A possible successful surgical result was terminated by a fatal hemorrhage from the tracheotomy wound. Retrograde catheterization of the aqueduct of Sylvius is a feasible, and not especially difficult, procedure. This may be employed

second cervical vertebra to a point 6 cm. above the external occipital protuberance. From this point the incision was carried in a semicircular fashion down behind the right ear to the tip of the mastoid. The ventricle was tapped immediately, and clear fluid was released slowly, under tremendous pressure. An indwelling cannula was inserted into the ventricle and allowed to remain in place during the entire procedure.

The musculoaponeurotic flap was then dissected from the bone overlying the cerebellum and the occipital lobe. The laminas of the atlas and axis were exposed, and the lamina of the atlas was removed. The bone was then rongeured away over the right side of the cerebellum and over the right occipital lobe up to and including the burr opening into the ventricle. The bone was also removed over the left cerebellar hemisphere.

The dura was opened with a fishhook incision over the cerebellum and the flap turned downward. The dura was opened over the occipital lobe, with the base of the flap parallel to the transverse sinus. Large

The tentorium was not sutured. The dura over the cerebellum and the occipital lobe was closed loosely with interrupted silk sutures. A drain was placed in the epidural space above the level of the foramen magnum. The subcutaneous layers and the skin were closed with interrupted silk sutures. The immediate postoperative condition was excellent.

Postoperative Course.—First Day: During the night the temperature and the pulse and respiratory rates increased, and the systolic blood pressure rose slightly. On the following morning respiration became rapid and labored. The spinal fluid pressure was 30 mm. of mercury, and the fluid was blood tinged; 30 cc. was slowly removed. Respiration immediately improved, and the systolic blood pressure was lowered.

The right lateral ventricle was tapped, and the fluid was noted to be under great increase in pressure. Approximately 100 cc. of fluid was slowly removed. Two hours later breathing again became labored and rapid, and there was a crowing type of respiration, with indrawing of the suprasternal structures. Emergency

Fig. 1.—Roentgenograms of the skull, showing the size and position of the calcified tumor.

veins passing from the occipital lobe to the transverse sinus were carefully cauterized and divided. The occipital lobe was displaced upward and laterad and the tentorium sectioned, so that the following structures were revealed: (1) the transverse sinus, (2) the superior longitudinal sinus, (3) the inferior longitudinal sinus, (4) the straight sinus and (5) both internal cerebral veins (veins of Galen).

The tumor could then be seen in the depths of the wound, just below the region of the pineal gland, the upper pole projecting beneath the pineal gland and obstructing the aqueduct. The tumor was whitish and the size of a flattened hen's egg, surrounded by dense adhesions and numerous tortuous vascular channels. A hypodermic needle was inserted into the tumor, and about 1 cc. of yellowish, cystic contents was evacuated. After tedious and prolonged dissection, it was concluded that approximately three fourths of the tumor had been removed. Although the patient's condition was excellent, it was decided to remove the remaining portion at a second stage, in view of the long operative siege.

laryngoscopy was performed, and a large, silk-woven catheter was inserted through the edematous vocal cords. Breathing immediately improved and became quiet. Two hours later the pulse became rapid; the face and neck were edematous; the face was flushed; the temperature was 104 F. (rectal), and the dressing was profusely wet. The dressing was reinspected, and a cotton wick was placed in the opening of the cannula. Meanwhile the patient was given 500 cc. of plasma and 500 cc. of whole blood. The chemical constituents of the blood were then normal, and the patient's condition was distinctly improved. The respiratory rate was still 36 to 40 per minute, but breathing was easier and without obstruction. Carbon dioxide and oxygen were given almost continuously.

Second Day: The patient's condition was somewhat improved. Respiration was still labored. There was slight movement to painful stimuli and definite movement when spinal drainage was carried out. The initial spinal fluid pressure was 22 mm. of mercury, and 40 cc. of clear, xanthochromic fluid was slowly removed. The respiratory rate immediately increased somewhat, and there was definite movement of all the limbs. The

Clinical, Technical and Occasional Notes

SPONTANEOUS IMITATIVE MOVEMENTS

Report of a Case

MAJOR H. H. GOLDSTEIN AND CAPTAIN RAYMOND SOBEL

MEDICAL CORPS, ARMY OF THE UNITED STATES

REPORT OF CASE

A white man aged 19 was admitted to the neuro-psychiatric service of a station hospital on Feb. 20, 1943. The patient, who was right handed gave as his chief complaint a mimicking disturbance of movement in the hand opposite the one used in carrying out voluntary action. The disorder had been present from birth. A farmer and ship's fitter, he occasionally went on alcoholic sprees, but drank less than a pint (500 cc.) once or twice a month. He smoked one package of cigarets daily.

Family History.—There was no history of familial or hereditary disease. His mother and one sister were left handed, and two other sisters were twins.

Personal History.—The patient had an attack of appendicitis six months prior to admission. He had had chills and fever, of unknown origin (not malarial), at the age of 15 years. At 12 years of age he was told by his physician that he had high blood pressure but that there was no evidence of nephritis. No symptoms referable to the gastrointestinal, urinary, respiratory and cardiovascular systems were present. There had been no injuries.

Present Illness.—Involuntary, simultaneous, "imitative" motion of the hand, and occasionally of the arm, on movement of the other hand or arm was first noticed by his parents when he was 4 or 5 months old. This symptom had persisted, with only slight improvement. The "imitative" movement mimicked the movement of the opposite hand or arm, but was less extensive; as a result he had always been somewhat clumsy in maneuvers which require dissociated motions of the arms, such as those used when a hammer is held in the right hand to hit a nail in the left hand (the patient's left hand swung in unison, but in miniature, with the right hand, so that he missed). Rarely, on his raising one arm, the other tended to follow. He had never noticed this phenomenon in his legs or feet but stated that he had always been somewhat slow in walking or running. It had not prevented him from working as a ship's fitter. Although it took him longer to perform tasks requiring dissociated dexterity of the hands, he circumvented the difficulty by fixation of one hand, so that it would be forced to remain in place. He was a good dancer and liked to "jitterbug." He had always been aware of weakness in his left arm and hand and stated that he could not "feel things" as well with the left hand and foot; by this he meant a stereognostic defect. As a result, he had used his right side practically to the exclusion of the left. To his knowledge, all the members of his immediate and distant family had normal coordination.

He had never noticed any disturbance of taste or smell or any diplopia, teichopsia, amblyopia or amaurosis. Tinnitus, as a result of his working near riveters,

had been present on occasion. He had had no abnormality or disturbance of sensation. The occurrence of convulsions, loss of consciousness and epilepsy was denied, as was the presence of shooting pains, girdle sensations, unsteadiness of gait or falling in the dark. Bowel and bladder sphincter control had always been intact, and sexual function was normal.

Although the patient had noticed improvement in dexterity during the past three years, he attributed it to practice in voluntary dampening and inhibiting of the contralateral movement. There had been no true remission or relapse. Aside from the weakness and asynergy of his left arm, no other symptoms were noted.

Neurologic Examination.—Cranial Nerves: First pair: Olfactory function was intact.

Second pair: The disks were normal, with no papilledema or optic nerve atrophy.

Third, fourth and sixth pairs: Extraocular movements were normal. The pupils were equal and active and reacted well to light and in accommodation. Slight hippus was noted in reaction to light. There was no nystagmus, paresis or paralysis. Ability to blink either eye singly was not tested.

Fifth pair: The trigeminal nerve was intact and normal. The corneal reflexes were active.

Seventh pair: The facial nerve was intact and normal.

Eighth pair: Bone conduction was less than air conduction. Sounds were not lateralized. Response to the Weber and Rinne tests were normal.

Ninth nerve: The gag reflex was present.

Tenth pair: There was no deviation of the palate.

Eleventh pair: Power in the sternocleidomastoid and trapezius muscles was normal and equal on the two sides.

Twelfth pair: The tongue protruded in the midline.

Motor Nerves: There was slight diminution of power in the upper and lower extremities on the left side, the loss involving all motions but being most noticeable in the distal portions and in the finer motions of the phalanges, wrist, toes and forefoot. Power in the muscles with cranial innervation was intact. The right side of the body was normal.

Tonus: There was slight but definite hypotonicity of the upper and lower extremity on the left side, with minimal spooning of the left hand. Rebound was more pronounced on the left side than on the right.

Coordination: Gait was normal. Turning to the right was poorly accomplished, whereas turning to the left presented no difficulty. There was slight swaying to the left in the Romberg test. Coordination was normal on the right side, but slight ataxia and intention tremor of the left arm were present in the finger to nose test. Asynergy and ataxia of small movements of the left hand were elicited on repetitive movements. There was no drift on extension of the arms.

538

in other cases of aqueductal obstruction. The Torkildsen procedure of ventriculostomy may likewise be tried. Torkildsen [4] reported some degree of success in 3 cases. Penfield [5] reported successful use of the method in a case of inoperable obstruction of the aqueduct.

The operative procedure of tentorial section in cases of tumors of the pineal region has been practiced and developed by Fay.[6] The approach gives sufficient accessibility to the tumor area and

4. Torkildsen, A.: New Palliative Operation in Cases of Inoperable Occlusion of Sylvian Aqueduct, Acta chir. Scandinav. **82**:117-123, 1939; abstracted, Acta psychiat. et neurol. **14**:221, 1939.

5. Penfield, W.: Torkildsen Procedure for Inoperable Occlusion of the Sylvian Aqueduct, Canad. M. A. J. **47**:62-63, 1942.

6. Fay, T.: The Management of Tumors of the Posterior Fossa by the Transtentorial Approach, S. Clin. North America **10**:1427-1459, 1930.

offers promise of successful surgical outcome in these hopeless cases. If the tumor should prove inoperable, roentgen therapy may be employed to better advantage, with division of the constricting ring of the tentorium.

It was interesting to note that no trace of tumor was evident post mortem. The position of the tumor indicated a probable origin from the posterior part of the velum interpositum. The tumor lay at the junction of the inferior longitudinal sinus, the straight sinus and the vena cerebri magna. The growth probably compressed the veins in this region, but whether the venous compression was the cause of the internal hydrocephalus is a matter of conjecture. The most probable cause was the obstruction of the aqueduct of Sylvius. The position of the tumor was similar to that reported by Balado and Tiscornia.[3]

Temple University Hospital.

Abstracts from Current Literature

Physiology and Biochemistry

THE EFFECT OF ERGOTAMINE TARTRATE AND NEOSYN-
EPHRIN HYDROCHLORIDE ON THE WORK CAPACITY OF
HUMAN MUSCLE. GEORGE C. KOTALIK, GEORGE L.
MAISON and CARL PFEIFFER, Am. J. M. Sc. **206**:503
(Oct.) 1943.

The authors proposed to determine, if possible,
whether therapeutic doses of ergotamine tartrate would
consistently produce muscle weakness in normal persons.
The Maison ergograph was used to the point of fatigue
to measure the work capacity. Ten thoroughly trained
subjects were used after a training period varying from
three to fourteen months, during which time the muscles
of each arm were worked to fatigue six days a week.
The work ability was tested at the height of the action
of the drug ninety minutes after the intramuscular in-
jection of 0.25 to 0.75 mg. of ergotamine tartrate, or
fifteen to thirty minutes after the intramuscular injec-
tion of 4 to 10 mg. of neo-synephrin hydrochloride. In
general, no significant decrease in work output occurred
after the intramuscular injection of ergotamine tartrate.
Subjective symptoms due to ergotamine tartrate were
surprisingly few, even with doses of 0.75 mg. The most
significant observation was the increase in work capacity
after the intramuscular injection of neo-synephrin hydro-
chloride. The authors conclude that the muscle weak-
ness occasionally reported from the use of ergotamine
tartrate in cases of migraine headache cannot be due
entirely to the drug.

MICHAELS, Medical Corps,
Army of the United States.

EFFECT OF PHYTONCIDES UPON PROTOZOA. B. TOKIN,
Am. Rev. Soviet Med. **1**:237 (Feb.) 1944.

Phytoncide is the name applied to the volatile sub-
stances produced by plants in their life cycle and
endowed with strong bactericidal and protistocidal
properties.

Tokin states that "small amounts of a paste of freshly
macerated onion, garlic or other plant emit enough
phytoncides to kill all exposed unicellular organisms
within 1-5 minutes." The species of protozoa most
thoroughly investigated was Paramecium caudatum.
Phytoncide was found to be common in many plants
investigated, and the author states that apparently "the
effect of phytoncides upon bacteria, fungi, or protozoa
is biochemical in nature." Such factors as the plant
source of the phytoncide, the distance (1-1.5 cm.) be-
tween the phytoncide and the test object and the rate of
dissipation of the vapor modify the results of the ex-
periments.

GUTTMAN, Philadelphia.

ACTION OF PHYTONCIDES UPON INFUSORIA. A. KOVA-
LENOK, Am. Rev. Soviet Med. **1**:239 (Feb.) 1944.

Kovalenok reports that phytoncides produced a lethal
effect on several species of free-living infusoria, on some
flagellates and on a parasitic infusorium found in the
pig intestine. A phytoncide from one plant applied for
equal lengths of time to various species of infusoria
varied in the mechanism of their action. The species

of protozoa was the determining factor. The effect,
however, was always lethal for the protozoa.

The author concludes that the experiments on pro-
tozoa may be helpful in investigating the action of phy-
toncides on cells and tissues of multicellular organisms.
The results may suggest a practical application of
phytoncide therapy to the control of pathogenic protozoa.

GUTTMAN, Philadelphia.

EFFECT OF PHYTONCIDES ON RABBITS. I. TOROPTSEV,
Am. Rev. Soviet Med. **1**:242 (Feb.) 1944.

Toroptsev subjected healthy rabbits, 6 to 10 months
old, to vapor from freshly prepared onion paste. The
treatment was given for four minutes, ten times a day,
for ten consecutive days. Fresh onion paste was em-
ployed for each treatment. The animals were killed at
various times—one, five and fifteen days after the last
inhalation.

There were an inflammatory reaction of the respira-
tory organs and stimulation of the reticuloendothelial
system, the cells of which were phytonotropic in rabbits
which were killed one and five days respectively after
the termination of the inhalations. In the rabbits killed
fifteen days after termination of exposure to the phy-
toncide the only abnormality was persistence of swelling
of the Kupffer cells. From this the author concludes
that the liver probably served as a barrier, since it still
exuded an odor of onions.

The author concludes that the inhalations of phy-
toncides in high concentrations produced slight, and
entirely reversible, changes in the tracheobronchial tree,
the liver and the kidney of the rabbit.

GUTTMAN, Philadelphia.

THE EFFERENT PATHWAY FOR PUPILLARY CONTRACTION.
P. W. NATHAN and J. W. ALDREN TURNER, Brain
65:343, 1942.

Nathan and Turner present evidence that two separate
pathways for efferent pupilloconstrictor fibers must
exist. The usually accepted pathway for pupillocon-
strictor fibers is that in which the fibers run from the
nucleus of the third nerve with the oculomotor nerve to
the inferior oblique muscle and branch off to the ciliary
ganglion. Distal to this ganglion they form several
short ciliary nerves, which run through the sclera, form-
ing the ciliary plexus, which innervates the sphincter
muscle of the iris. If this were the only pathway
available, its interruption should result in failure of the
pupil to react either to light or in convergence. The
authors, however, cite the experiments of Foerster,
Gagel and Mahoney in which pupillary contraction in
convergence persisted after removal of the ciliary gan-
glion. This observation, the authors believe, indicates
that the accepted pathway subserves only the light reflex
and that another pathway exists for the reflex constric-
tion of convergence. In addition, Nathan and Turner
report 10 clinical cases from the literature and 2 cases
from their personal observations which demonstrate a
differential paralysis of the pupillary constriction to
light. The criteria established to prove that the lesion

Reflexes: All the deep reflexes were present in normal degree on the right side and were slightly increased throughout on the left side. Abdominal reflexes were present but were easily exhausted on both sides. There were equivocal fanning and dorsiflexion of the large toe on plantar stimulation, and frequently spontaneous bilateral and unequivocal extensor plantar signs appeared in tests of motor function of the lower extremities. The Chaddock, Oppenheim and Hoffmann signs were absent. A blow on the ball of the foot produced flexion of the toes on the left side only (Rossolimo sign).

Sensory Status: Pain, touch, temperature and vibration senses were intact throughout.

Stereognosis: The patient recognized the depth and shape of coins with the right and the left hand, but poorly with the left. He failed to distinguish the configuration of a paper clip with the left hand. He pointed out arcs of a circle well with both arms but distinguished them poorly with the fingers of the left hand.

Two point discrimination: Epicritic sensibility was diminished on the left side. Two points separated 1 cm. were identified as one over the pads of the fingers of the left hand, whereas discrimination of points separated as much as 3 mm. was present in the right hand. Discrimination sense was diminished over the entire left half of the body.

Associated Movement: There was no adiadokokinesis in gross motions at the wrist or at the metacarpophalangeal joints. However, repetitive movements of the phalanges on the left side were impaired, asynergic and ataxic.

The disturbance of motion was illustrated by the following test: On flexion of the first and second phalanges of the fingers of the right hand there was involuntary, simultaneous and "imitative" flexion of the first and second phalanges of the left hand. This movement occurred in miniature, the phalanges on the left side moving only 1 cm. or so. This "imitative" movement was present to a lesser degree when the voluntary movement was carried out with the left hand. Flexion, extension or rotation at either wrist produced contralateral movement of like nature, but of lesser degree. In the opposite extremity, the "imitative" movement being more pronounced in the left extremity. The more proximal the movement, the less apparent was the phenomenon; this was also true of axial movements. The patient stated that he had been able to inhibit the involuntary axial motions at the shoulder by practice, and hence they were observed only when he felt that he was not being watched. Although he had never noticed the "imitative" movement in his lower extremities, it was as apparent in the toes as in the hands. However, movement of the toes of the left foot did not produce movement of the toes of the right foot, as in the case of the arms. This was also true of the seldom observed "imitative" motion of the axial joints. There was dissociation of movement in the phalanges of the left foot which was not present in those of the right

foot; with grasping motions of the small toes of the left foot, the large toe went into dorsiflexion, whereas on the right side the toe was plantar flexed with the remaining digits.

The greater the patient's awareness of the motions carried out, the less evident was the "imitative" motion. Old, habitual patterns, such as writing and buttoning the shirt, were more productive of contralateral motion. No contralateral movement was attained in involuntary motion stimulated reflexly; that is, production of a knee jerk on the right side did not produce a contralateral knee jerk. The Magnus and De Kleijn reflex and crossed extensor reflexes were not elicited, and there was no evidence of decerebrate activity.

Aphasia: There was no anomia, alexia, agraphia or acalculia, either expressive or receptive. The patient was right handed and had no directional confusion. He followed seriatim commands and performed seriatim mental calculations. No semantic disturbances were evident. He had had difficulty in pronouncing his second name, Edmund, in grade school, but this did not persist.

Psychiatric Status.—There was no evidence of any psychiatric disorder. No hysterical phenomena were noted.

Systemic Examination.—The only relevant physical signs were a rough protruberance, about 2 by 2 cm., in the right occipital region, which underlay a sebaceous cyst, and enlarged inguinal lymph nodes secondary to epidermophytosis.

The blood pressure was 118 systolic and 76 diastolic. The temperature, pulse and respiration were normal. The blood count revealed 4,780,000 red cells, with 85 per cent hemoglobin, 6,850 white cells and a normal differential count. Urinalysis revealed that the specific gravity and the microscopic constituents were normal, and the reactions for sugar and for albumin were negative. The sugar, cholesterol and nonprotein nitrogen contents of the blood were within normal limits.

Roentgenographic examination of the skull revealed nothing abnormal. Spinal puncture showed normal pressure and normal dynamics. The fluid was clear. The Wassermann reaction of the fluid was negative; the colloidal gold curve was 000000000; the sugar level was normal; the protein measured 35 mg. per hundred cubic centimeters, and the cell count revealed 2 lymphocytes per cubic millimeter.

SUMMARY

An apparently congenital, unremitting disease of the central nervous system in a 19 year old white man was manifested by inability to dissociate motor function of one side from that of the contralateral side. Spontaneous, simultaneous, involuntary and seemingly imitative motion of a lesser degree occurred in the part contralateral to that voluntarily moved. Mild hemiparesis, incoordination, cortical sensory signs and slight reflex changes were demonstrable in the left extremities.

The hypertensive twin was by far the more dynamic of the two; he was more aggressive, more energetic, more conscientious and more active socially than his normal brother. The authors suggest that the element of rivalry, with constant repressed hostility, was the motivating factor of the latter's success; on the other hand, it may also have been responsible for his hypertension.

The evidence presented in this report suggests that renal ischemia is an incidental, and not a causative, factor in the pathogenesis of clinical hypertension. The similarity in the heredity and the early environment of the identical twins in this case stresses the divergence in personality drives as a possible cause of the hypertension present in one of them.

AUTHORS' ABSTRACT.

THE ANALYSIS OF A CASE OF COMPULSIVE MASTURBATION IN A CHILD. ELISABETH R. GELEERD, Psychoanalyt. Quart. **12**:520, 1943.

Geleerd shows that the compulsive masturbation in the young child whose case she reports had several determinants:

1. The child looked on her body as part of her mother's body. The mother's absence created a fear that her needs would not be satisfied, a fear which manifested itself through physical excitement; for this excitement masturbation was the physical outlet. It meant for the child that the mother was taking care of her.

2. The masturbation represented the little girl's fantasy of having a penis. She masturbated with this imaginary penis and showed it off in her exhibitionism.

3. All her fantasies—the positive and negative Oedipus fantasies, the fantasy of being beaten by the mother, the mother in the aggressive role of castrating her child, and the child's preoccupation with her genitals because she had no penis—found an outlet in her masturbation.

PEARSON, Philadelphia.

HYPNOSIS IN TREATMENT OF NEUROSIS DUE TO WAR AND TO OTHER CAUSES. CHARLES FISHER, War Med. **4**:565 (Dec.) 1943.

Fisher used hypnosis as a rapid form of therapy for traumatic neuroses. The therapeutic results were mostly in the nature of symptomatic cures, and none of the patients was cured in the sense that he had genuine insight into the unconscious mechanisms responsible for his symptoms. Hypnosis exerts a therapeutic effect in three ways: (1) by the use of direct suggestion; (2) by producing abreaction of repressed affect, and (3) by bringing into consciousness dissociated or repressed thoughts after the resistances have been broken through. The third way is indispensable for a genuine cure but is most difficult to carry out. The results obtained through the use of hypnosis with pure suggestion and the bringing about of abreaction should not be minimized, particularly if a little interpretation of the unconscious material can be included.

PEARSON, Philadelphia.

MINNESOTA MULTIPHASIC PERSONALITY INVENTORY. CARLETON W. LEVERENZ, War Med. **4**:618 (Dec.) 1943.

In an experience of over one year the author found the Minnesota multiphasic personality inventory valuable in the neuropsychiatric service at the station hospital, Fort Snelling, Minn. It revealed hitherto unsuspected abnormalities in personality and assisted the clinician in arriving at an earlier and more accurate impression of the degree of abnormality. The clinical impression was not always corroborated by the score obtained on the inventory, but the inventory made the examiner more aware of the existence of one or more abnormal changes in the personality which required evaluation.

PEARSON, Philadelphia.

ANXIETY NEUROSIS IN COMBATANTS. C. P. SYMONDS, Lancet **2**:785 (Dec. 25) 1943.

Symonds describes the anxiety neurosis as of two types: The first type can be explained by the theory of conflict. This assumes that the sense of anxiety arises from the conflict between fear of a given war situation and a sense of duty and loyalty. The second type is described as due to exaggeration of a normal fear response under extreme stimulation. Symonds believes the problem in cases of the second type is a question of the degree of affect, just as it is in many cases of severe depressive states. Such affect is generated in situations which do not cause similar fear in the so-called normal person. Thus, the occurrence of such a neurosis depends a great deal on the individual sensitivity to trauma of a psychic nature. Actually, the author believes, most war neuroses are of a mixed type, in which conflict and anxiety play part of the role and exaggerated fear the other part. The awareness of the condition may vary as much in a neurotic state as it does in any number of normal ranges of emotion. Therefore the degree of consciousness of one's conflict is not in itself a sign of how abnormal the conflict is, though it may influence the course and prognosis of the illness.

McCARTER, Philadelphia.

Diseases of the Spinal Cord

PROTRUDED INTERVERTEBRAL DISK AND HYPERTROPHIED LIGAMENTUM FLAVUM: ANALYSES OF FIFTY SURGICALLY TREATED CASES. JOSEPH C. YASKIN and ANTHONY S. TORMAY, Am. J. M. Sc. **206**:227 (Aug.) 1943.

Yaskin and Tormay review 50 verified cases of protruded intervertebral disk. Thirty-one patients were males and 19 females, the average age being 39.6 years. In more than half the cases there was a history of trauma, which was slight as a rule. The average duration of symptoms was four and one-third years, and remissions were observed in 32 cases. The initial symptom was usually located in the back (middle and paravertebral portions). The pain was usually deep and was aggravated by bending, sneezing and coughing. In 42 cases the lesion caused major disability. The following abnormalities were encountered: diminished lordotic curve, 47 cases; tilting of the pelvis, 36 cases; muscular spasm, 48 cases; alteration of the knee jerk, 9 cases; alteration of the achilles reflex, 21 cases; hypesthesia, 4 cases, and a positive Lasègue sign, 42 cases. Tenderness of the sciatic nerve, often observed in cases of neuritis, was rarely seen. Myelographic study with air was a reliable diagnostic procedure. The operative results appeared gratifying in 36 of the 50 cases.

In differential diagnosis orthopedic, primary neurologic and visceral disease, systemic processes and psychalgias should be considered. In no case in which the diagnosis is reasonably certain should operation be regarded as desirable unless (1) previous adequate orthopedic and other treatment has been tried without improvement in the disability; (2) there is moderate to

is in efferent, rather than in the afferent, path are as follows: The pupil on the normal side must contract when the affected eye is illuminated; (2) the affected pupil must not constrict to light or dilate in darkness, either directly or consensually; (3) both pupils must contract normally in accommodation and convergence and dilate afterward, and (4) the lesion must be known to be peripheral.

The 2 personally observed cases are reported in detail: In 1 case a penetrating shell fragment came to rest on the floor of the middle fossa, just over the foramen ovale, and in the other a fracture occurred, with compression of the sphenoid fissure. Both cases fulfilled the aforestated criteria. From this evidence the authors conclude that the Argyll Robertson pupil may be due to injury of the efferent pathway to the pupil and that two efferent pathways for pupillary contraction, one subserving the light reflex and the other accommodation-convergence synkinesia, must exist. Four possible routes which the efferent fibers, which conduct the impulse to contract in accommodation and convergence, may take are considered: (1) with the sympathetic fibers, (2) via the extraocular muscles, (3) via the optic nerve, and (4) via the nasociliary nerve. The authors present evidence eliminating each of the aforementioned paths as a possibility. Finally, they offer the hypothesis that these fibers run from the third nucleus to the episcleral ciliary ganglia, thence relaying to the ciliary body, without passing through the ciliary ganglion.

SHENKIN, Philadelphia.

Psychiatry and Psychopathology

THE SPIROGRAM IN CERTAIN PSYCHIATRIC DISORDERS. JACOB E. FINESINGER, Am. J. Psychiat. **100**:159 (Sept.) 1943.

Finesinger describes a method of scoring irregularities in the spirographic record. To arrive at a simple numerical score the method employs seven variables: sighing respirations, major and minor fluctuations of the upper and lower lines of reference and point off the upper and lower lines. Tracings were obtained from 100 psychoneurotic patients, 60 schizophrenic patients and 103 normal controls.

The highest mean score was obtained for patients with anxiety, and the lowest mean score, for patients with schizophrenia and for normal subjects. The mean values for patients with hysteria and for patients with reactive depressions fell between these two extremes. The differences in the scores for patients with anxiety and the scores for patients with schizophrenia and for normal subjects were statistically valid. Sighing respirations and major fluctuations were most frequent for patients with anxiety and least frequent for normal subjects. These differences were statistically significant. The only statistically significant difference between the scores for schizophrenic patients and the scores for normal control subjects was found in the lower frequency of fluctuations from the upper line among schizophrenic patients.

FORSTER, Philadelphia.

ORGANIZATION OF PSYCHIATRIC SERVICES IN BATTLE AREAS. N. N. TIMOFEEV, Am. Rev. Soviet Med. **1**:264 (Feb.) 1944.

Timofeev stresses the necessity of mobile psychiatric units for use in theaters of operation. The special field psychiatric unit has five main functions: (1) to classify psychiatric casualties which come from the front; (2) to treat men who can be helped within four to six

weeks; (3) to prevent evacuation of mildly neurotic patients, (4) to provide psychiatric consultation to medical installation and rehabilitation centers, and (5) to provide consultation to field hospitals with small psychiatric wards.

Psychiatric patients should be grouped in special hospitals as near the front as possible. Group therapy and the psychiatrist's understanding help to restore self respect and morale.

GUTTMAN, Philadelphia.

REHABILITATION OF THE WAR WOUNDED IN THE SOVIET UNION. A. N. SUKHOV, Am. Rev. Soviet Med. **1**: 293 (April) 1944.

Soviet law divides veterans into three classifications for pension purposes: (1) totally handicapped persons needing hospitalization; (2) totally handicapped persons not needing hospitalization, and (3) veterans now unfit for their previous occupations but capable of less exacting work. The amount of pension depends also on military rank and the veteran's former wages. A war invalid continues to receive a pension, in addition to his wages, when he returns to work.

Rehabilitation facilities and pensions are administered by the People's Commissariat of Social Security of the U. S. S. R. Facilities include research institutes, laboratories, polyclinics, schools, rest homes, sanatoriums and cooperative societies. War invalids attend free training schools and receive pay during the period of training. Individual consideration is given to the veteran's course of retraining, as well as to his job assignment. By August 1943, 91 per cent of the partially disabled veterans in the Soviet Union were employed.

Retraining units are incorporated into many hospitals and cover a wide variety of industrial and agricultural occupations. These units supplement the veterans' vocational schools and boarding schools, which are under medical supervision.

Prostheses are manufactured and fitted by the state. Sukhov states that a patient who uses a prosthesis is usually able to work in from two to four months after the amputation. Particular attention is given to men who have lost both arms or both legs, including the fitting of special prosthetic devices and occupational training.

Wounded veterans receive certain privileges, including an annual vacation and full sickness benefit. They also have some tax exemptions and priorities on consumer goods. Mutual aid societies contribute further forms of assistance to veterans.

GUTTMAN, Philadelphia.

HYPERTENSION IN ONLY ONE OF IDENTICAL TWINS. MEYER FRIEDMAN and J. S. KASANIN, Arch. Int. Med. **72**:767 (Dec.) 1943.

Friedman and Kasanin report a case of hypertension in one of identical twins. Studies included routine physical examination, psychologic assay, electrocardiographic study and determination of the renal blood flow and the glomerular filtration rate for each twin.

Renal function tests revealed that the blood flow in the kidneys was similarly reduced in the normatensive and in the hypertensive twin and that the glomerular filtration rates were also similar. Electrocardiograms for the hypertensive twin revealed definite evidence of myocardial damage, while the tracing made for his brother was essentially normal. Aside from the cardiovascular differences, the contrasting personalities constituted the only striking difference noted in the twins. The healthy twin was always more robust physically and intellectually more alert than the hypertensive twin.

due to sulfadiazine, of which 86 per cent were renal in character.

The mortality rate of only 3.1 per cent for the treated patients and the absence of any fatalities or residuals which might be ascribed to the drug justified the use of massive doses of sulfadiazine.   MICHAELS,
Medical Corps, Army of the United States.

THE USE OF PHYTONCIDES IN THE TREATMENT OF INFECTED WOUNDS. I. V. TOROPTSEV and A. G. FILATOVA, Am. Rev. Soviet Med. **1**:244 (Feb.) 1944.

Toroptsev and Filatova report their observations on 11 patients who were given repeated phytoncide treatments. Seven of the patients had amputation of the arm; 1, of the thigh, and 3, of the foot. Eight of the wounds were purulent and contained streptococci, white staphylococci and other bacilli. In 2 patients amputation was complicated by gas gangrene, and in 1 patient, by frostbite. The flora of the wounds of the last 3 patients could not be determined. Osteomyelitis of the extremities was present in over 40 per cent of the patients. All the patients were anemic and had an elevated erythrocyte sedimentation rate. Prior to phytoncide treatment, all lesions showed evidence of inflammation, in some cases with a marked odor; edema of the soft tissues was also present.

The authors employed the following technic: Onions of high quality with bronze, dry peel were used. The part chosen was first examined for the activity of its phytoncides on protozoa. One third of the onion was freed from the dry leaves and ground quickly. The resulting paste was immediately placed in a Petri dish set 2 to 3 cm. from a previously prepared slide containing 1 drop of water with protozoa. The dish was covered. When the onion was sufficiently active, all the protozoa died in one to three minutes. Next, a glass vessel, with a diameter equal to that of the wound, was prepared. It has been the authors' experience that short chemical glasses are most suitable for wounds of the upper extremities and Koch dishes for stumps of the thighs.

Vaporization was performed daily as follows: The paste of one or two onions was placed in a previously prepared dish or glass and applied so that the surface of the wound did not come in direct contact with the paste. The stump was wrapped in several layers of cotton, so that the paste was protected from direct contact with the air. Vaporization was administered for ten minutes, usually in two intervals of five minutes each, at first with the paste of one onion and five minutes later with the fresh paste of another onion. After vaporization the wound was dressed. Before each treatment the wound was cleaned.

Toroptsev and Filatova state that after the initial phytoncide treatment, all wounds, without exception, become rose colored, instead of gray. A few patients had slight capillary hemorrhage; at the same time, they no longer complained of pain. After the second treatment purulence subsided, and the wound was no longer malodorous. The tissues of the injured extremities were bright red, but edema of the soft parts became more noticeable. In five days all wounds showed extensive epithelization. Edema of the soft parts rapidly disappeared, and many patients became free of pain.

The authors state that positive results were not obtained with all patients. Although the inflammatory process was arrested, there was a decided increase in granulation, with lack of epithelization in some parts of the wound. Such wounds contained ligatures and sequestrums, and the authors conclude that "phyton-

cides reduce the infection by freeing the potent o healthy elements of connective tissue."
GUTTMAN, Philadelphia.

ELECTRIC SHOCK THERAPY FOR PSYCHOSIS WITH SPECIAL REFERENCE TO DEMENTIA PARALYTICA. M. C. PETERSEN, Proc. Staff Meet., Mayo Clin. **19**:278 (May 31) 1944.

Petersen reports on the results of treatment of 458 patients with electrical shock. There were no deaths. Fifty-eight per cent of the patients with effective psychoses have adjusted socially, and the condition of 23 per cent has improved greatly. Of the patients with schizophrenia, 32 per cent of those with catatonia adjusted satisfactorily, as compared with 17 per cent of the patients with hebephrenia and paranoia.

Sixteen patients with dementia paralytica were treated with electrical shock. Improvement was noted in all these patients but was not pronounced in those with agitated and depressed states. The treatment was used only as an adjunct to fever therapy or to chemotherapy.
ALPERS, Philadelphia.

PENTOTHAL SODIUM ANESTHESIA IN NEUROLOGIC SURGERY. BARNES WOODHALL and ELIZABETH GOODMAN, War Med. **4**:556 (Dec.) 1943.

Woodhall and Goodman have used anesthesia induced with pentothal sodium, with air or combined with oxygen, in 378 varied neurosurgical procedures. With certain qualifications in respect to age and the degree of intracranial pressure, it has proved an ideal anesthetic agent for use in intracranial surgical procedures. Their experience with it in neurosurgical operations associated with shock suggests its potential value for major cranial wounds.
PEARSON, Philadelphia.

MANAGEMENT OF MENINGOCOCCIC INFECTIONS AT THE STATION HOSPITAL, FORT BENNING, GEORGIA. LOUIS OCHS JR. and MICHAEL PETERS, War Med. **4**:599 (Dec.) 1943.

The plan of treatment for meningococcic infections at the Station Hospital, Fort Benning, Ga., was as follows: Four grams of sulfadiazine was given orally as the initial dose, followed by 1 Gm. every four hours. A one-sixth molar solution of sodium lactate was given for the first forty-eight hours. The daily fluid intake was 3,000 to 4,000 cc. The urinary output was maintained at 1,500 cc. or over in twenty-four hours. All manifestations of drug toxicity and of shock were treated as soon as they arose. Serum or antitoxin was given when necessary, as were repeated lumbar punctures for the relief of intracranial pressure.

Seven patients so treated for seven days all recovered clinically and bacteriologically. All the patients had pain in the joints or in the tendons for six weeks after recovery.
PEARSON, Philadelphia.

IMPROVEMENT OF VISUAL AND OTHER FUNCTIONS BY COLD HIP BATHS. ARTHUR H. STEINHAUS and ALBERT KELSO, War Med. **4**:610 (Dec.) 1943.

A cold hip bath produces a striking temporary improvement in visual functions involving binocular vision, in visual acuity, in critical fusion frequency, in tapping rate and in eye to leg muscle reaction time. The improvement usually lasts two and one-half hours but may continue for at least six hours if no meal is eaten. There is no after-depression.

major disability, and (3) attacks of major or of moderate disability for considerable periods frequently recur.

MICHAELS,
Medical Corps, Army of the United States.

THE PROBLEM OF HERNIATED NUCLEUS PULPOSUS IN THE MILITARY SERVICE. WILLIAM G. HAYNES, War Med. **3**:585 (June) 1943.

The symptoms of herniated nucleus pulposus consist of pain in the back or legs, along the distribution of the sciatic nerve, which follows a minimal amount of trauma and is made worse by coughing or sneezing. Examination reveals tenderness of the spinous process overlying the suspected disk, a positive Laségue sign and diminution in or absence of the achilles reflex.

Haynes reports on a series of 21 men with herniated nucleus pulposus. Eleven were discharged from the Army because of disability arising from a condition which existed prior to induction. Ten patients were operated on, and the protruded intervertebral disk was removed. None of these men returned to full duty. One was discharged with a diagnosis of psychoneurosis. Haynes attributes his high percentage of good results to a number of factors, which include: (1) careful selection of the patient for operation (he notes particularly that in the Army only men who are psychiatrically sound should be operated on for herniated nucleus pulposus); (2) use of the preoperative, operative and postoperative schedules and care which he describes, and (3) the fact that all the patients were strong, healthy young men.

PEARSON, Philadelphia.

Peripheral and Cranial Nerves

HEMATOPORPHYRINURIC NEURITIS. LEWIS A. GOLDEN, Am. J. M. Sc. **206**:474 (Oct.) 1943.

Up to 1940 less than 200 cases of hematoporphyrinuric neuritis had been reported in the literature. Golden reports the case of a white man aged 47, who was first seen in 1942 in a semiconscious, moderately delirious condition, occasionally groaning with pain and apparently dehydrated. Muscular weakness of the extensors of the wrists and feet was obvious. In 1940, after a laparotomy, transient paralysis of the left arm occurred, which lasted about five days. Intermittent colicky pains persisted until the patient's admission to the hospital. Bowel movements remained regular until two days after his admission, when diarrhea, with an average of ten to twenty stools a day, occurred. Urinary retention developed. On admission to the hospital, the blood pressure was 214 systolic and 110 diastolic, the pulse rate 120 and the temperature 99.4 F. The fundi showed moderate arteriosclerosis. Motor weakness of both upper and lower extremities was obvious, and wrist drop was apparent. On August 11 the urine was wine colored and showed a positive reaction for urobilinogen in a dilution of 1:258 and a positive reaction for uroporphyrin type 1. On August 12 the patient began to show bulbar symptoms, and the next day he died. The pia-arachnoid was grayish white and showed scattered areas of thickening, 1 to 5 cm. in diameter. The anatomic diagnosis was cardiac hypertrophy, acute ulcerative colitis and chronic peritonitis. The leptomeninges were greatly thickened, and there was patchy loss of ganglion cells in the cortex. The clinical diagnosis was hematoporphyrinuria, of unknown cause. The disease appears to be a metabolic disturbance intimately connected with the synthesis and degradation of hemoglobin and is usually associated with the excessive excretion of porphyrin in the urine (porphyrinuria).

MICHAELS,
Medical Corps, Army of the United States.

PAIN IN THE SHOULDER GIRDLE, ARM AND PRECORDIUM DUE TO FORAMINAL COMPRESSION OF NERVE ROOTS. S. S. HANFLIG, Arch. Surg. **46**:652 (May) 1943.

Pain in the shoulder, arm or precordial region may be due to compression of a cervical nerve root. This type of pain is related to movements of the neck and is made worse by sudden increase of intraspinal pressure, but not by movements of the shoulder. Diagnostic aid is obtained by roentgenograms and by temporary application of overhead suspension traction.

The following conditions must be considered in the differential diagnosis: disorders of the shoulder joint, cervical rib syndrome, scalenus anticus syndrome, rupture of a cervical nucleus pulposus, tumor of the spinal cord, hypertrophic osteoarthritis of the cervical portion of the spine, cervical strain of postural origin, angina pectoris and psychoneurosis.

Overhead suspension traction relieves the pain due to narrowed intervertebral foramen with encroachment on a radicular nerve, such as occurs with arthritis of the cervical portion of the spine, but it is ineffective in cases of rupture of a cervical nucleus pulposus and of tumor of the cord; it increases the pain in cases of cervical rib and the scalenus anticus syndrome. In cases of psychoneurosis atypical responses are seen.

Head traction is a valuable therapeutic method; it may be applied as intermittent stretch by means of an overhead suspension device, with the patient in the sitting position, or as continuous traction by means of Sayre's sling, with the patient recumbent. The author prefers the former method because it is more rapid in its effect and does not require hospitalization.

LIST, Ann Arbor, Mich.

Treatment, Neurosurgery

TREATMENT OF ONE HUNDRED AND THIRTY-FOUR CASES OF MENINGOCOCCIC INFECTION WITH MASSIVE DOSES OF SULFADIAZINE. BRUNO A. MARANGONI and VINCENT C. D'AGATI, Am. J. M. Sc. **207**:67 (Jan.) 1944.

Marangoni and D'Agati analyze 134 consecutive cases of meningococcic infections encountered at a station hospital since March 13, 1942. The patients were all men, 10 of whom were Negroes. The ages varied from 18 to 44 years. Sulfadiazine therapy was employed, with the following basic plan of dosage: initial dose, 8 Gm.; second dose (two hours later), 5 Gm.; third and fourth doses (at four hour intervals), 4 Gm.; subsequent doses, 3 Gm. every four hours. The optimal sulfadiazine concentration in the blood was considered to be between 15 to 20 mg. per hundred cubic centimeters. In cases of fulminating meningococcic infection a 5 per cent solution of sodium sulfadiazine was given intravenously as the initial procedure.

The doses of sulfadiazine were much greater than those ordinarily employed. A mortality of 6.7 per cent (9 patients) was encountered for the entire group. Three patients exhibited meningococcemia with the Waterhouse-Friderichsen syndrome, and a fourth patient had meningococcic meningitis. Eight of 20 patients (40 per cent) treated with sulfanilamide had one or more toxic manifestations. A total of 28 per cent of the patients presented complications of various types

Society Transactions

NEUROPSYCHIATRY AT THE GREAT LAKES
TRAINING STATION

General Aspects. LIEUT. COMDR. F. C. SOUTHWORTH (MC), U.S.N.R.; LIEUT. L. D. BOSHES (MC), U.S.N.R., and LIEUT. R. J. LEWINSKI, H(S), U.S.N.R.

A study of 14,000 men with neuropsychiatric coloring over a period of time revealed a constitutional psychopathic state, chiefly of the inadequate personality type, in 39.75 per cent, psychoneurosis in 25.12 per cent, mental deficiency in 12.75 per cent, enuresis in 6.20 per cent, a post-traumatic syndrome in 3.71 per cent, migraine in 2.77 per cent, somnambulism in 2.62 per cent, convulsive disorders in 2.51 per cent, illiteracy in 1.76 per cent, neurologic disorders in 1.40 per cent, alcoholism in 0.75 per cent, immaturity in 6.49 per cent and a history of psychosis in 0.17 per cent.

The importance of the Naval training stations in making decisions for retention or rejection of Navy personnel is emphasized. Primary screening of the recruit on arrival, with subsequent study in a specialized unit, if the case warrants further work-up, is discussed. The psychologic division of the unit is described. The work of the American Red Cross as the official social service agent of the Navy is praised. The use of trial duty for men with borderline conditions is emphasized, as are the duties of the various boards who eventually sit in session on neuropsychiatric cases. Standards of acceptance and their variations are considered and it is emphasized that more neuropsychiatrists are needed for the solution of current problems, as well as for treatment of Navy personnel who present discipline problems or who have returned from combat zones.

Special Aspects. COMDR. H. S. MILLETT (MC), U.S.N.R.; LIEUT. A. H. FECHNER (MC), U.S.N.R., and LIEUT. S. B. CUMMINGS, H(S), U.S.N.R.

The work of the Medical Survey Board in the study of men presenting problems of discipline who have had considerable service and of men who have been in combat is discussed. The number in either group is increasing gradually. The Board is aided in its final decision by personal observation of the members and by the information at hand, which includes the health record, the service record, the social service report and the brig psychiatrist's report. It is important to learn whether or not the present condition existed prior to entry into the service and whether military service has or has not aggravated the illness.

The two large groups of cases reviewed included cases of the constitutional psychopathic state, which made up 64.5 per cent of all cases reviewed by the Board. The subgroups comprised cases of emotional instability, 50 per cent; inadequate personality, 10.4 per cent, and schizoid personality, 41 per cent.

A small number of cases of the so-called war neuroses are reviewed; recommendations for discharge or retention were based on combat experience, number and severity of engagements, personal injury, personal fatigue and loss of sleep, anorexia and other symptoms. Almost two thirds of the returning men with war neuroses were recommended for shore duty—temporary or permanent—and the other one third was discharged from the Navy.

Neuropsychiatric and Psychologic Aspects of Discipline. LIEUT. J. L. KINNEY (MC), U.S.N.R.; LIEUT. COMDR. B. N. BENGTSON (MC), U.S.N.R., and LIEUT. L. A. PENNINGTON, H-V(S), U.S.N.R.

All prisoners admitted to the brig undergo a physical and medical examination, a psychologic study, a psychiatric interview and a "sociologic" study. Recommendations may include (1) action by the discipline officer, (2) study in the hospital along medical or psychiatric lines, (3) retention in the brig for further study by the staff and (4) referral of the prisoner to the neuropsychiatric unit for additional study.

Men admitted to the brig usually include those with "borderline" states who have been passed by draft boards, induction centers and psychiatric examiners; other persons admitted include those with emotionally immature, unstable or inadequate personalities.

Final dispositions may include (1) for men likely to adjust in the future, routine disciplinary action with restoration to duty; (2) for chronic repeaters, routine disciplinary action followed by discharge, in keeping with their records; (3) for men who are mentally ill but may be discharged into their own custody, a medical discharge, and, finally, (4) for the psychotic or the emotionally unstable patients, study in the hospital with final disposition.

DISCUSSION ON PRECEDING PAPERS

DR. GEORGE E. WAKERLIN, Chicago: As a physiologist, may I point out that constitutional psychopathic states and psychoneuroses unquestionably have physiologic and neurologic bases? Moreover, there is experimental evidence supporting this point of view. For instance, changes can be produced in various visceral organs by stimulation of certain portions of the cerebral cortex. There are of course connections between the cerebral cortex and the hypothalamus, which is the headwaters of the autonomic nervous system. Stimulation of the anterior hypothalamus in animals produces parasympathetic effects in various visceral structures, such as slowing of the heart, increased gastric secretion and increased gastrointestinal motility, and stimulation of the posterior hypothalamus gives sympathetic effects, such as an increase in heart rate, decrease in intestinal motility and increase in blood pressure. Lesions of the hypothalamus produced in the dog have given rise to gastric ulcer, which can be prevented by previous subdiaphragmatic vagotomy. Also, an appropriately placed lesion in the hypothalamus gives rise to the pseudoaffective state in animals. Prefrontal lobotomy, as is known, has been reported to reduce worrisome states in the human subject. These facts point to neurophysiologic bases for the psychoneuroses and the constitutional psychopathic states, as well as a neurogenic factor in peptic ulcer, mucous colitis, hypertension and other conditions.

The studies indicate that a cold hip bath might be used in those aspects of warfare and industry that involve monotonous routine duties demanding acute vision and alert performance.

PEARSON, Philadelphia.

REACTIONS TO SULFONAMIDE COMPOUNDS. THOMAS F. FRIST, War Med. **5**:150 (March) 1944.

Frist reviews 186 cases of reactions to sulfonamide compounds. Among these are fever, cutaneous manifestations, hematuria, renal colic, azotemia, leukopenia, hepatitis, polyarthritis, conjunctivitis, cardiac complications, psychoses, peripheral neuritis, nausea and vomiting.

He describes cases in which there developed fever, agranulocytosis, renal damage, hemolytic anemia and interstitial myocarditis, and suggests the following simple rules, which, if carried out, will enable sulfonamide compounds to be used with relative safety:

1. The patient should be observed at least every other day for rash, conjunctivitis, jaundice, diarrhea, arthritis, drug fever and chills. 2. Urinalysis for the presence of red blood cells should be made every third day. 3. There should be adequate intake and output of fluid. 4. Sodium bicarbonate should be administered with each dose of the sulfonamide compound. 5. If the patient has had a previous toxic manifestation, he should be tested for reactions before being treated with the drug.

PEARSON, Philadelphia.

who take the job as routine, we are inclined, like Dr. Hamill, to feel that a man who shows disinclination, together with emotional instability and other complaints, is better out of than in the service. For every candidate examined at the induction station, we can, in the allotted five or ten minutes, easily carry out the screening tests, which will relieve the reception station of any casualty which might develop. The war neuroses, however, are unpredictable. Even though the speaker stated that no direct relation exists between the intensity or length of exposure and the neurosis, I should like to ask him his opinion of the length of training which should precede the exposure to war service. It seems to me that all men should receive a thorough training before they are sent out to combat duty, a policy which, in my opinion, would reduce the incidence of war neuroses. Since the Navy is already inducting youths of 17, a preinduction training for boys of from 16 to 17 could be established and the final training given after the age of 18, an arrangement which would produce far better soldiers.

DR. DAVID SLIGHT, Chicago: I have been astonished to hear of the large number of men discharged because of enuresis and somnambulism. In private and clinic practice one does not see many adults with such disorders, nor do I recall hearing that such a large percentage of men was discharged from the armed forces in World War I for these reasons. However, the percentage of men being rejected and discharged with all forms of neuropsychiatric disorders is greater in this war, and this may be a reflection of changes in medical standards and in the completeness of the examinations. Have any of the speakers had an opportunity to look up the statistics for men discharged with such disorders of personality maturity in World War I?

One cannot but note the high psychiatric standards adopted by the Navy. Likewise, the large percentage of cases classified under various subdivisions of the general heading "psychopathic personality" is noteworthy, as compared with the statistics for the Army.

Psychiatrists in the services should be watchful with regard to attaching psychiatric diagnoses to men who are proving inapt or troublesome. In many cases of such difficulty the standards of judgment and evaluation should perhaps not be psychiatric as one ordinarily understands the term. Thus, many men may be disgruntled, anxious to get out of the services, dissatisfied with their particular branch of the services, resentful of their immediate officers or assignments or upset by news from home. These factors may indeed be disturbing and interfere with the man's happiness, willingness or interest so that he appears inapt, if not troublesome, and is considered inefficient or undesirable for further service. I wonder, however, whether the psychiatrist should be the agent for the discharge of such men, or whether action for discharge should not properly be made through other channels and on grounds other than medical. In many such cases a discharge on medical grounds may have unfortunate reverberations later in claims for hospital care and pensions, as Dr. Hamill has suggested.

LIEUT. COMDR. F. C. SOUTHWORTH: In reply to Dr. Haus's question, most of these men had considerable experience in the Navy prior to combat. The average man in the Navy has recruit training; subsequently, he may or may not go to the service school, where he has additional training over a considerable period, and then prior to combat experience he has duty aboard ship. Most of the men have considerable experience before being sent into actual combat.

With regard to Dr. Haus's comment about the careful examination at the induction station at Great Lakes, a very small number of men come before our board from the Chicago Induction Station and from the northern stations in general. A large percentage of our men with severe disturbances come from other areas of the country, where the general level of education and social background is lower than here; so if we had only the Chicago and comparable stations, the need for our unit would almost cease to exist.

With regard to the comments of Dr. Gerty and Dr. Wakerlin concerning the number of rejectees and the question of whether too many or too few are screened out, it is the feeling of almost all the psychiatrists with whom I have talked and come in contact that few men are rejected who ought not to be. Although such men may, apparently, be able to carry on a normal life under civilian conditions, bitter experience in the last war has shown that many who broke down in the service became neurotic invalids for life. My associates and I attempt to some extent to eliminate men who we think will break down under battle conditions. We believe that few are rejected who ought not to be rejected. On the other hand, we are constantly under pressure to accept men who ought not to be accepted. The Man Power Commission, of course, is also under tremendous pressure. It has to provide men and has a hard time doing it. When we turn down a large number of men, the Commission doesn't like it; so we are always fighting to maintain our standards against that kind of pressure. At present we are probably keeping many men whom we ought not to keep, rather than rejecting many who should not be rejected.

As to the figures for the percentage of rejections, our data do not include the percentage of rejections at the induction stations, and I do not have that figure. Our own figures for rejections for neuropsychiatric reasons vary from time to time, according to the manpower situation, the number of men being inducted and the stage of the drafting process. For some time our figure was between 4 and 5 per cent of all recruits rejected for neuropsychiatric reasons alone. At certain times it crept up and approached 8 per cent. In recent months there has been a tightening of standards, apparently as a result of the Surgeon General's complaints that too many psychiatric casualties were developing in the war zones, and the general level has dropped again to between 4 and 5 per cent. That value, however, again is artificial because the number of rejections among Negroes is much higher. The proportion of rejections among Negroes varies anywhere from 8 to 10 per cent of the total number which we receive, so that if the Negro group were eliminated the level would drop probably to 4 per cent or a little less.

As Dr. Hamill indicated, the conditions of life on shipboard constitute an important factor, and one much more important in the Navy than in the Army because of the close contact into which the men are thrown. The problem of enuresis is a major one on a ship. The problem of homosexuality also becomes significant in a situation in which the contacts are so close and so long continued, and it is important to eliminate men with such a personality disorder.

I doubt whether enuresis and somnambulism are more common now than in the last war, but statistics are not accurate enough to prove the point. In the last war little effort was made to weed out men with such disorders, and a great many of them served in combat and, we believe, swelled the ranks of the invalids whom the government hospitalized for periods of years after the war. The diagnosis is made more frequently now because psychiatrists on the induction boards are trying to detect as many cases as possible. I doubt whether

Neurophysiologists and biochemists are making considerable progress in understanding the metabolism of the cells of the central nervous system, including those of the brain, as well as the mechanisms of synaptic transmission. The time will come when sufficient physiologic information will be available so that psychiatrists will understand what is happening in the brain and the nervous system of patients with psychoneuroses, constitutional psychopathic states and similar conditions.

Lieutenant Fechner and his associates mentioned that many psychiatric patients give family histories indicative of a hereditary factor. It should be remembered that any hereditary factor must operate through a physiologic mechanism. Thus, diabetes mellitus, although possessing a definite hereditary factor, usually operates through the physiologic mechanism of a decrease in the amount of insulin secreted by the islets of Langerhans. By the same token, constitutional psychopathic states and psychoneuroses must operate through certain physiologic and neurologic mechanisms.

In all three papers treatment was mentioned, and of course these men are in need of treatment. But more important than therapy is prophylaxis. As a citizen and a taxpayer, as well as a humanitarian, I am greatly interested in seeing these conditions prevented in the next generation, and I believe more can be done in this respect than is being done at present. After all, these conditions undoubtedly arise in part from the stimuli supplied by the environment. A more favorable control ought to be exercised over the environment of the children. Thus, a greatly expanded mental hygiene program is needed in this country, and psychiatrists should impress the general public more forcibly in regard to this need. I believe that if a better mental hygiene program existed within and outside the schools, many potentially unstable children would not grow up to have psychoneuroses and constitutional psychopathic states. I wonder, too, whether these conditions are not in part attendant on lack of proper sex education during adolescence and early adulthood. More should be done in this direction, particularly in the schools, although a good deal of education of the public in the matters of sex will be necessary before this is possible.

I should like to ask Lieutenant Commander Southworth whether he has any figures on the percentage of inductees rejected for neuropsychiatric reasons. Also, what percentage of the total number of rejectees does this constitute? I have seen various figures, published and unpublished, and they do not agree.

Dr. Francis J. Gerty, Chicago: I am informed that there is another person to be heard from; so I shall try not to take too much time. In private psychiatric practice, of course, the screening is about 100 per cent effective—all the patients referred have some nervous or mental trouble. The problem of the Navy is a different one. There seem to be two schools of thought on the matter: According to one school, the screening lets through too many persons who should have been eliminated; according to the other, too many persons have been screened out who should have been let through. I talked recently with a psychiatrist who is in charge of screening at another Naval training station. He expressed the belief that men were screened out who should have been let through. He seemed to have swung to a view the reverse of that presented here tonight. He expressed the opinion that the psychiatric examinations were tending to encourage a certain type of malingering, that is, simulation of neuropsychiatric conditions. Possibly there is merit in this view. Not long ago a man who was discharged from the Navy came to me to tell me that he had a terrible stigma.

He had been assigned to one of the so-called suicide training units, having something to do with landing boats. He went to the chaplain during his period of training and said he was homosexual. Shortly thereafter he was discharged from the Navy. However, he did not like the type of notation on his discharge. When it became necessary to find a job, he did not like to tell employers why he had been discharged. He wanted to know what he could do to have this "mistake" rectified, as he actually was not homosexual. Of course there was nothing I could do about it. I note in Lieutenant Commander Southworth's paper that there is reference to the malingering of enuresis. I had not heard of that before. Possibly, neuropsychiatric information is spreading among the military forces and is being made use of in this manner. However, if a man malingers, it is questionable whether he will do very well in military service. I was interested to note that the truth of something which I think most psychiatrists had suspected has been demonstrated in Lieutenant Fechner's paper, namely, that some of the men with psychoneuroses seem to stand combat conditions well and that their difficulties center about things that most people are not in the habit of regarding as real, rather than about the real troubles. It is questionable as to how far we psychiatrists should go in the matter of returning to duty persons who we know have neuropsychiatric difficulties of one sort or another. It may be that the man will succeed under conditions of military service, even in combat areas, and he may seem at times to be good material for this purpose. That of course is not the long view of the matter. Every now and then I see men in the veterans hospital who got along fairly well under actual service conditions but who have been charging for it ever since. I do not say, however, that this constitutes the great bulk of patients who had service in the first world war. Many of them seem not to have contributed much to the military effort during the war but charge the same price afterward. I should be much interested to hear Dr. Hamill discuss the matter of enuresis.

Dr. Ralph Hamill, Chicago: Of course, with this wet crowd, the Navy, and with Davy Jones' locker right alongside, one could find all sorts of excuses for wetting the bed. Malingering seems rather serviceable, I should say. However, any one who takes advantage of it would not make a good companion on such a ship as I went out on two weeks ago. There were 300 men on it, and there was no room for any one who did not fit in and who did not want to do his part. Consequently, in my work on the induction board, I vacillate between the impression that a fellow is trying to fool me and the feeling that I don't care if he is trying to get out of service, I want to let him out; the vast majority of the men of his type are better out than in the Navy. After service, we taxpayers will pay for the care of men whose records state that their difficulty was increased in service.

Dr. L. W. Haus, Madison, Wis.: It has been my privilege to work on the induction board for the last three years, and, although I did not hear all of the first paper, I can say that my associates and I have seen all the conditions which Lieutenant Commander Southworth mentioned. I am surprised at the great number of men with neuropsychiatric conditions encountered at the naval station, for it is my policy and that of my associates to be as rigid as possible at the induction examination. I believe we do not discharge any man who should be in the service, but, in view of the great number of certified disability discharges which have resulted from the careless examinations of psychiatrists

in bed, she would within half a minute be seen to have become largely immobilized. Her facial expression ceased to be animated; her eyes stared unwinkingly. She answered questions in a dull, monotonous voice, often making mistakes in her answers to simple questions about her age and address. During this phase, she was capable of adding 2 and 2 or 4 and 4, but made mistakes in adding 9 and 4 and 7 and 8, or added the figures quite irrationally, without any evidence of thought.

The limbs, exhibited the waxy flexibility characteristic of certain catatonic states associated with "schizophrenia." The arms, if placed in a grotesque and uncomfortable position, remained unsupported, apparently without fatigue, until either they were replaced or she was ordered sharply to put them down.

At first these episodes occurred several times a day and lasted from five to forty minutes. They ended about as quickly as they began; that is, she would blink, rub her eyes, look animated, move about in bed and perhaps then slip out of bed and run about the room, with the childish gestures appropriate to her age. When she was asked what had been happening to her, she could never say more than that she "had felt queer and could not talk right."

After two months these episodes occurred only occasionally, when I ceased to see her; then she went to her home in the Middle West. About two years afterward I heard from friends that she was well but apparently very nervous. I was, therefore, not surprised when, in September 1941, I was again consulted because ever since her original illness she had been subject to a rhythm of fluctuating energy and emotion. This had settled into a constant pattern: a period of nine to thirteen days of elation, in which she looked very bright, was greatly animated and extremely restless, rarely sat down (and then only on the edge of her chair), had bursts of talk, did her lessons at top speed, and far more than was required, and slept little. On many occasions she was known not to have slept at all for six days and nights, this without any sign of fatigue but with loss of weight.

At the end of this period of elation she would within one day begin to slow up, grow quiet, become shut into herself, answer in monosyllables in a low, flat voice, work slowly at her lessons and have the general air of a middle-aged, faded nun. This state lasted from two to three weeks and was always followed by a period of elation, such as has been described.

Clearly, she had a manic-depressive psychosis, with a rapid swing in mood of curiously timed regularity. There was no history of emotional instability in her family. For years she had made engagements according to the way she knew she would be when the day came.

They had not been able to keep her at boarding schools because in her elated periods she had kept all the girls in the dormitory awake by constant talking all night and every night, and had often insisted at 3 o'clock in the morning on saddling her horse and riding across country.

In 1941 I expressed the opinion that it might be possible to cure the episode with electrical treatment, but that the treatment had no prophylactic value for the future. I therefore did not think this therapy would be of benefit and did not administer the treatment until the spring of 1942. She has received only five treatments, each given at the beginning of a period of elation. They have always restored the normal rhythm of sleep and produced tranquility of emotion and behavior.

No treatment has been given, or required, since April 1943. She has been successfully maintained in boarding school, and her family report that she is better than she has ever been. In fact, since May 1943 the difference between her period of elation and her period of depression could be detected only by members of her family, who themselves said that perhaps they saw something unusual only because they were looking for it.

DISCUSSION

Dr. Gerald R. Jameison: Dr. Kennedy's case is extremely interesting. However, I cannot see that this case of encephalitis, followed shortly by sharply defined, alternating periods of elation and depression, proves that there is an organic basis for cyclothymia. As a matter of fact, I do not believe that the clinical picture of the mood reaction is that of cyclothymia, at least not in terms of the adult reaction. It is quite evident that the patient had encephalitis, but it does not follow that because she has had a cyclic swing in mood since then her condition should be classified as manic-depressive psychosis. The disturbances of many children with encephalitis have been classified as schizophrenia, but I believe that most such conditions are organic, and not true schizophrenia, at least not in the clinical sense in which the disease is understood to exist in older people. However, there must be a physiologic factor in the usual cyclothymic reaction. In a single manic or a single depressive attack with complete recovery, it is easy to note that personality factors reacting to environmental stress have psychologic significance, needing evaluation and treatment. With the cyclothymic patients, however, irrespective of such factors, once the persistent swing in mood begins, psychologic treatment, or in fact any type of psychotherapy, is, unfortunately, limited in value. The inevitable course of the cycle continues. In such conditions it is easier to suspect that inherent elements of biologic nature influence the patient's personality. Some children are born with a tendency to be active, lively and aggressive, these manifestations being recognizable almost from the day the child is born. Other children are quiet, passive and subdued. How these tendencies are influenced by the environment probably has much to do with how the patient handles his emotional patterns. However, although Dr. Kennedy's patient had an organic condition producing a clinical picture which resembles a so-called functional psychosis, one cannot as yet believe that functional psychoses are actually of organic origin.

Dr. Renato Almansi: In connection with Dr. Kennedy's experience, it may be of interest to report a case of chronic encephalitis in a clinic patient who has been under observation for several months. The patient, a woman aged about 35, had encephalitis about twenty years ago and now shows postencephalitic parkinsonism. Since that time she has had oculogyric crises, with a rhythm of one, and sometimes two, attacks a week. They last from one to six hours and are accompanied by an obsessive attack, which begins with the onset of the crisis, lasts throughout and ends with it. If she is in the street, she feels that people are looking at her, and she runs home and shuts herself in. If she is in the house, she feels that people are looking through the window; so she pulls down the blinds. Even then she cannot rid herself of the idea that people are peeping under the blinds. This puts her in a severe state of anxiety, which lasts throughout the crisis. She has fairly good insight into the fact that there is no reason for this obsessive idea. I have seen mention of the same condition by von Economo (Encephalitis Lethargica, Berlin, Urban and Schwarzenberg, 1929, page 170), and Dr. Bernhard Dattner told me that he has seen a num-

there actually are more persons with these disturbances, but more men are being rejected for milder types of neurosis than was practiced in the last war. With respect to the point that the Navy seems to have more psychopaths than the Army has, it is true that there is a decided tendency, at least in our station, and I think in the Navy in general, to list as psychopathic, with emotional instability or with inadequate personality, a great many persons who in civilian practice would be called neurotic. Their symptoms are those of a neurosis, but they are called psychopaths because of the underlying condition which contributed to the development of the neurotic symptoms. They could quite well be called neurotic. The group of psychopathic states is heterogeneous and includes many conditions which would not ordinarily be considered in a discussion of psychopathic personalities as such. I think that the figure is rather high, even if it is not 40 per cent of the population. Just a word in conclusion about prophylaxis. Certainly, the treatment of these neuropsychiatric conditions has not been brilliant. In view of the great number of persons with such conditions in the population at large, and the fact that so many of them have not been seen by physicians or by clinics, psychiatrists should certainly lay more stress on the importance of the mental hygiene movement and make an effort to prevent these disorders in every possible way, particularly by more adequate training in the early years of life.

NEW YORK NEUROLOGICAL SOCIETY AND NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY

CLARENCE P. OBERNDORF, M.D., *President, New York*

Neurological Society, Presiding

Joint Meeting, Jan. 11, 1944

Neuro-Ophthalmologic Conditions: Moving Pictures. Presentation of Cases. DR. S. P. GOODHART and DR. B. H. BALSER.

CASE 1.—A 13 year old girl showed a congenital condition characterized by an abnormal movement of the right upper lid accompanying all forms of movement of the lower jaw, including voluntary movements (Marcus-Gunn phenomenon); in repose there was no apparent abnormality.

CASE 2.—From a boy aged 9 years a large cerebellar neoplasm was removed. Among the classic signs of the tumor was so-called skew deviation; on lateral gaze the homolateral eye turned downward and outward; the other eye synchronously turned upward and inward. This phenomenon is associated with lesions of the brain stem. Its presence here with a cerebellar process was doubtless due to secondary compression of the brain stem. With removal of the tumor the phenomenon disappeared.

CASES 3, 4 and 5.—Patients with multiple sclerosis showed various types of nystagmus.

CASE 6.—A patient with Weber's syndrome (alternating oculomotor hemiplegia) showed contralateral (right) hemiplegia with homolateral complete paralysis of the left third nerve; the vascular lesion was in the basis pedunculi at the level of the red nucleus on the left side.

CASE 7.—Unilateral Duane's syndrome is a congenital entity rarely encountered in which there is fibrosis of the levator palpebrae superioris muscle and of the external rectus muscle of one or of both eyes. This results

in widening of the palpebral fissure as the eye turns laterally and in narrowing as it turns medially, as well as in limitation of lateral gaze in the affected eye.

CASE 8.—A patient with bilateral Duane's syndrome showed the characteristic phenomena, with involvement of both eyes.

CASE 9.—A patient with myasthenia gravis presented some of the ocular phenomena observed with this disease. The favorable influence of neostigmine was demonstrated.

CASE 10.—A patient with postepidemic encephalitis presented the unusual phenomenon of inability to open the voluntarily closed eyes; in order to do so the patient was obliged to carry out the associated movement of extreme hyperextension of the head.

CASE 11.—A patient with neuromyelitis optica presented evidence of involvement of the optic nerves, optic chiasm, optic tracts and spinal cord.

CASE 12.—A patient with extensive Recklinghausen's disease (neurofibromatosis) also presented, as a result of congenital absence of the posterior orbital wall, ptosis of the left eye and pulsating enophthalmos of the left eye, which was synchronous with the heart beat. On pressure over the left jugular vein in the neck, the eye bulged forward in a series of steps synchronous with the pulse. On coughing, the eye popped violently forward into an exophthalmic position, and the extraocular movements were limited to those of the internal rectus and superior oblique muscles. A roentgenogram showed absence of the greater wing of the sphenoid and a small portion of the lateral part of the lesser wing. Loss of movement of the left eyeball was due to absence of a bony wall for attachment of the extraocular muscles.

DISCUSSION

DR. H. A. RILEY: This presentation shows remarkably well the enormous material and interesting cases Dr. Goodhart has at the Montefiore Hospital. Much of it was so rapid that it was difficult for me to follow the pictures, and many features of the examinations were not sufficiently clear for me to understand entirely the various conditions presented.

The patient with unilateral nystagmus interested me. I did not think the condition was entirely unilateral. There seemed always to be some movement in the eye contralateral to the direction of gaze. This is not an uncommon condition; nystagmus predominant in the homolateral eye is frequently much more noticeable than in the eye contralateral to the direction of the gaze; this is especially true in patients with multiple sclerosis.

DR. S. P. GOODHART: Dr. Riley's suggestion that the pictures should be more slowly projected is in line with my own idea; I usually arrange for careful technical showing of the films so that I, myself, am not obliged to "chase the patients" as they are presented on the screen.

Postencephalitic Cyclothymia: Report of a Case. DR. FOSTER KENNEDY.

K. M., now aged 19, at the age of 9 years was referred to me by Dr. William St. Lawrence. She had fever, headache and a stiff neck; at the beginning of the illness there were prolonged light stupor, double vision and a count of 68 cells per cubic millimeter of spinal fluid. Dr. Tilney and I had no hesitation in making a diagnosis of encephalitis. The child was in bed five weeks. When the stupor had cleared, a peculiar condition became manifest. When she was sitting up

opposed forces throughout nature. The nervous energy, the tonic energy, to use a familiar term, of the sympathetic nervous system is the accelerator, and the parasympathetic system acts as the brake. There is a good deal of evidence, some of which I cited in my paper entitled "The Hypothalamus: Pacemaker of the Organism" (J. A. M. A. **30**:2092 [May 25] 1940), that the hypothalamus maintains the balance between the energy of one system and that of the other. I do not know why in certain persons the balance becomes upset from time to time. It may become upset, as Dr. Jameison said, by precipitating circumstances, the influence of environmental distress. It also becomes disturbed for reasons of which one has no knowledge, and which produce such despair, if it is a depression, that the patient to integrate his own personality must find an explanation. And who cannot find some explanation in the circumstances of his life? A young woman says that she is in despair because she has been "a bad mother," in spite of the fact that her husband says she has been one of the best. A tailor in Newark says he is in despair because "his son is running his tailoring business to the dogs." Show him the books: It makes no matter. That is his stand, and he is going to fight it out on that line if it takes all summer! It helps him to have a reason for his terrible internal feeling, but one would be blind if one were to accept the patient's explanation of his trouble.

Dr. Goodhart stated that the manic-depressive psychosis is not regular in rhythm but that has not been entirely my experience. I can give Dr. Goodhart the case histories of at least a dozen persons I have seen in the last thirty years who have had a regular rhythm of depression and elation, many, oddly enough, a seasonal one. A physician's wife in this city is always elated for six months and depressed for six months. She has been like that for fifteen years. I have now a patient under my care who has been in that condition for the last eight years—five or six months one way and five or six months the other. I do not understand the reason, but I do know that one does not feel the rotation of the earth, one does not feel any of the things that are causing one to be alive and one is apt to think that forces of which one is unconscious have therefore no valid existence.

Platybasia: Report of a Case. Dr. B. C. Meyer (by invitation).

A woman aged 47 was first admitted to the Mount Sinai Hospital in May 1942, with the complaint that during the preceding year she had had attacks of burning pain in the back of the neck two or three times a day, accompanied by a sensation of difficulty in breathing and swallowing. For six months she had noted hoarseness, unsteadiness of gait, clumsiness and numbness of the upper limbs and impairment of memory. Examination revealed bilateral optic nerve atrophy, which was interpreted as primary. In addition, she displayed bilateral horizontal nystagmus, corneal analgesia and signs of involvement of the pyramidal pathways and of cerebellar function. Roentgenographic examination of the skull showed enlargement of the sella turcica with erosion of the dorsum sellae and the posterior clinoid processes. A tentative diagnosis of an intrasellar neoplasm was made, and roentgen ray therapy was instituted, without benefit. On readmission in September 1942, she displayed "onion peel" hypalgesia of the peripheral portion of the face, as well as hypalgesia and thermohypesthesia of the neck and body as low as the fourth dorsal dermatome. At this time the optic nerve atrophy was considered sec-

ondary. In addition to the signs referable to the pyramidal tract and the cerebellar dysfunction previously noted, there was impairment of deep sensibility in the upper extremities, especially on the right. Reexamination of the roentgenogram of the skull showed that the odontoid process extended above the so-called Chamberlain line. There was no construction or distortion of the foramen magnum. The protein content of the spinal fluid was 54 mg. per hundred cubic centimeters. The patient refused permission for ventriculographic study and was discharged. Eight months later she was readmitted because of severe exacerbation of symptoms. She had become bedridden and was unable to feed herself. Sensory disturbances now extended as far down as the tenth dorsal dermatome. The remainder of the examination revealed accentuation of the previous observations. Ventriculographic examination, performed by Dr. B. Schlesinger, showed symmetric hydrocephalus, with upward and forward displacement of the fourth ventricle. Dr. Ira Cohen performed a suboccipital craniotomy and cervical laminectomy, which revealed a large cyst lying within the cisterna magna and containing about 25 cc. of clear fluid. It extended upward between the cerebellar hemispheres, occupying the position of the vermis, and downward through the foramen magnum to the level of the atlas. The medulla oblongata was observed lying in the cervical canal as far down as the second cervical vertebra. A transverse ridge was noted opposite this vertebra, indicating that the latter had pressed against the zone of transition between the medulla and the cord. The neuraxis appeared somewhat softened at this point. The spinal nerves were noted to run cephalad to their foramens of exit. The cyst was emptied, and as much of its wall was removed as possible. After operation the patient showed remarkable improvement. She was able to walk and could care for herself. Examination before her final discharge revealed optic nerve atrophy, nystagmus, corneal analgesia, slight intention tremor and mild weakness of the legs. The other signs had disappeared.

The designation of the malformation in this case by the term platybasia is obviously an oversimplification. Disorders of the occipitoatlantal junction are rarely seen in pure form. Usually, there are encountered various combinations of anomalies, which may include platybasia or basilar impression, brevicollis (the Klippel-Feil deformity), the Arnold-Chiari malformation, malpositions of the axis in relation to the atlas and occiput, and syringomyelia. The patient presented here revealed the association of the Arnold-Chiari deformity, a cyst of the cisterna magna and a mild degree of platybasia. Clearly, the last condition did not contribute directly to the production of the symptoms; yet the association of this mild deformity with other anomalies which did produce signs and symptoms indicates the importance of postulating such additional deformities in cases of platybasia in which the roentgenographic evidence is lacking.

DISCUSSION

Dr. Richard Brickner: Two clinical comments might be made: first, that attention was drawn to the search for the correct diagnosis by the relative shortness of the patient's neck; and, second, that in my experience the clinical picture shown by this woman is rare. The patient had a midline neurologic picture involving both the cervical portion of the cord and the medulla. Both sides of the face showed sensory involvement; the spinothalamic pathways from the arms and the upper part of the trunk were damaged on both sides, and there were also bilateral signs of injury to

ber of cases of obsession occurring during oculogyric crises.

DR. ISRAEL STRAUSS: Dr. Kennedy's case is of great interest because it opens an opportunity for speculation in a field in which psychiatrists are most ignorant. The patient unquestionably had encephalitis. The encephalitis progressed to a subacute stage. A pathologic process must have occurred in her brain which probably produced organic alterations. The changes may have been reversible, but it is known that in cases of the subacute form many of the lesions persist. There often follows a disturbance of function, which may produce a psychic disorder. After a period, that disturbance may again induce another change in physiologic function. The problem here, as I think Dr. Kennedy hints, is concerned with what has developed in the hypothalamus. It is possible that the lesion is there. It is known that psychic states can be produced by stimulation and other experimental means in that region of the brain. The hypothalamus is an area from which emotional excitement may be aroused. In the case under discussion the period of exaltation was followed rhythmically by a period of depression or a trancelike state. The problem is what can so alter the biologic activity of that part of the brain as to produce such wavelike swings of mood. Are they of chemical or of physical nature? How does electric treatment disturb the process to such an extent as to cause a return to the normal? Dr. Jameison believes that in these cases of recurrent manic-depressive psychosis a fundamental condition—he calls it the personality—must be present, and I should say there must be something inherently and fundamentally important in the biologic makeup of the individual patient. This something, of which one knows nothing, must facilitate the physiologic changes that produce these cyclic swings in mood. The importance of Dr. Kennedy's case lies in showing that search for conflicts in the unconscious or that the influence of environment will not of itself solve the problem of the innermost workings of the brain.

DR. RICHARD BRICKNER: It is worth while to recall the remarkable observations Foerster made while he was operating on a tumor of the third ventricle with the use of local anesthesia. When he touched various areas on the walls of the ventricle, the patient went into something resembling the manic state, which instantly ceased when the tactile stimulus was released. This reaction could be elicited or abolished at will. Foerster eventually reported 6 or 7 cases in which he obtained such responses.

DR. S. P. GOODHART: Dr. Kennedy has given an instructive and interesting discourse, with the presentation of an unusual case. I should hesitate, however, to call this case one of cyclothymia, as one understands the term. While there is often regularity, with rhythmic and predictable recurrences in adults, this does not seem to hold true in early life. What impresses me as striking and suggestive of a postencephalitic psychosis is just what is seen in the case of this girl; she showed not only episodes of somatic signs but regularity in the recurrence of psychic episodes, the basis being evidently an organic lesion, such as occurs with encephalitis. Recurrence and periodicity are characteristic of epidemic encephalitis. For example, I remember a patient at Montefiore Hospital with oculocephalogyric episodes which lasted exactly thirteen hours. Dr. Kennedy's case, likewise, raises the question of the relation of the psyche and the soma: I recall a patient who was admitted to Montefiore Hospital with all the distinctive features of postencephalitic parkinsonism; superimposed

on the classic somatic signs were definitely psychogenic features. At my suggestion, one of my associates, Dr. Leo Stone, undertook hypnosis. After four or five interviews, during which hypnosis was induced, the patient emerged from his abnormal mental state, and the suppression of normal associated movements, rigidity, typical parkinsonism facies and excessive salivation had all disappeared. The transformation was striking. No further effort was made to hypnotize him. After a few weeks, however, he lapsed into his former parkinsonian state.

I wish to emphasize my own skepticism with regard to Dr. Kennedy's case. Though the alteration of mood is often predictable in adults, the swing of mood and behavior as presented by this child places the case on a pathophysiologic basis, such as is observed in epidemic encephalitis.

DR. C. P. OBERNDORF: The picture described by Dr. Kennedy is not one which is recognizable as that of cyclothymia. The patient had regular alternations of depression and elation every two weeks, which could be predicted. The ordinary concept of cyclothymia (and I presume by cyclothymia Dr. Kennedy means manic-depressive psychosis) is that of an unpredictable disorder, in which a person may not for many years have an attack either of elation or of depression. Dr. Kennedy's case has not been duplicated in my experience or in my reading. But I cannot quite follow his reasoning regarding the etiologic factors in cyclothymia. He mentioned the history of encephalitis in his case and he reasoned that a lesion affecting the hypothalamus in early childhood was responsible for the cyclothymia. In few cases is encephalitis in childhood followed by a manic-depressive psychosis. On the other hand, manic-depressive psychosis, or cyclothymia, occurs annually in thousands of people who have never exhibited any hint of an encephalitic disorder. I understood Dr. Kennedy to say that a lesion occurring in the hypothalamus at the time of the original illness was the basis for the disorder. Dr. Kennedy gave this child, now grown, electric shock therapy. Presumably it changed the lesion, or the residual malfunction of the hypothalamus, so that the young woman recovered. I should be interested to know just how Dr. Kennedy feels that this lesion in the hypothalamus was cured by electric treatment.

DR. FOSTER KENNEDY: This case is on the borderline of important things. It has to do with what I call the pathology of forces, which I believe will be the pathology of the future.

Dr. Oberndorf spoke of a lesion and asked me how electric treatment—which I did not call electric shock treatment—could change the lesion. We physicians have been so accustomed to consider that nothing exists if it cannot be seen under the microscope that by learning to see we have become blind.

I believe that Dr. Almansi, who described an obsessional state in association with an oculogyric crisis, had a case similar to mine. I have seen many supersaturated solutions of despair crystallize out an obsessional compulsion neurosis: a preoccupation with numbers; a preoccupation with cleanliness; a paranoid fear of ghosts, coming on in attacks, throughout life, associated with an underlying depression, the existence of the depression being often denied by the patient. Patients do not easily admit that they are mentally ill. They often translate their depression into a somatic symptom or into a compulsion neurosis. I think that the health, the stability, of the organism depends on the unstable equilibrium existing, as it does, between

and become infected, healed to form a small button of tissue, obviously not in need of operation. The patient died several weeks later, of an intestinal disorder. In the other case the delicate, tense sac became small and tough, so that plastic repair could be carried out without difficulty. The functional result in the cases of the 2 surviving patients has been excellent.

DISCUSSION

Dr. Byron Stookey: Dr. Putnam has given an interesting method of reducing the size of the sac, which otherwise would be inoperable. I think the method can be used advantageously in cases in which an operation is really indicated and in which the promise of repair is good. I question the wisdom of the operation in certain cases. I have never forgotten an experience about twenty years ago; a mother came into the old Vanderbilt Clinic with a girl 7 or 8 years old who was paraplegic and incontinent and had trophic sores over the buttocks; the mother was frantic. No doubt the mother, when the child was an infant, had begged the surgeon to do the repair. The repair was done satisfactorily; the mesodermal structures were covered over, but the defect in the nervous system, obviously, could not be repaired, and the child, then 7 or 8 years old, was completely paralyzed. I have made it a practice never to operate on a patient with spina bifida who has paralysis of the legs, particularly if a girl, because when there is paralysis, especially of the muscles below the knee, control of the bladder is seldom regained. Perhaps it is a *tour de force* on the part of the surgeon to improve such a situation locally, but I wonder whether it is surgical wisdom. I do not mean to detract from the skill of the procedure; Dr. Putnam has presented a useful method, and his choice of material has not been in his favor. Certainly, this method would make easier repair in cases of meningocele in which it is worth while to do anything, and it has opened a way by which advancing hydrocephalus, which is a common complication of a successful repair, may be treated. The method takes care of the hydrocephalus which has in a number of instances complicated a successful repair in a patient who can walk and has prevented a favorable outcome. In such cases this method offers a great surgical advance. I still question whether I should have operated in this case or in the second case, in which there seemed to be paralysis of both legs. The toes seemed to be dorsiflexed, as though there was pronounced flaccidity of the flexor muscle. Although the mother is anxious to have this child now, I wonder whether she will be anxious to have it ten years from now. That is merely a matter of philosophy, and it does not detract from the value of the operation.

Dr. H. A. Riley: I should like to ask Dr. Putnam how much of the choroid plexus can be destroyed by the endoscopic method and whether the plexus in the temporal horn can be reached by this approach.

Dr. C. P. Oberndorf: The philosophic question which Dr. Stookey raised is one which always confronts the surgeon and physician in a case of such an apparently hopeless condition. Just now I am reading "The Little Locksmith," a remarkable autobiography of a woman who lay on her back from the age of 5 to 15 years. She has produced a book throwing much light on the thoughts of the physically handicapped, and one which I think will live for many years. One cannot foretell how the child's mind will develop, and as physicians we should attempt to see how we can benefit the patient, rather than take the matter of life and death into our own hands. Physicians often see only a "case" in an afflicted person—sometimes even in a child, for whom the parents feel deeply. The very fact that parents put all their love and attention into such an object—and it is an animate object—seems to make the philosophy of Dr. Putnam valid. I hope I have not anticipated what Dr. Putnam may be about to say.

Dr. Tracy J. Putnam: To answer Dr. Riley's question first: It is usually possible to get all the choroid plexus down into the temporal lobe and into the foramen of Monro. The great bulk of the choroid plexus is in the glomus, in the body of the ventricle, and I am sure that something like 90 per cent of the secreting surface is in the glomus alone.

The point Dr. Stookey brought up is well taken. In the second case one leg was weak; the other was good, and there was good bladder control. When I recalled a patient on whom I operated ten years ago, who still has one weak leg in a brace but is a happy and intelligent child, I felt justified in operating in this second case. The third case was somewhat more problematic in that there was some weakness of both legs, but apparently sensation and bladder function were intact, and still are. The decision was more difficult; here, again, it looks as though this child were going to be the only one, and the parents were very anxious to have everything possible done; but perhaps I should not have acceded to their request. In my experience, it is difficult to know how much recovery of function will result from repair of a meningocele.

Aside from the question of function of the legs and sphincters, there is another criterion of operability in cases of meningocele, as well as in cases of hydrocephalus, which I think has received insufficient attention. I feel strongly that with either condition one should consider carefully the psychologist's estimate of the child's ability, and I feel much more opposed to operating on a baby who does not measure up to the performance expected from its age than I do in performing an operation where there is trouble with one leg. When there is weakness in both legs, the procedure becomes questionable indeed.

Defect in Synthesis of Acetylcholine in Patients with Myasthenia Gravis. Dr. Clara Tordo (by invitation) and Dr. Harold G. Wolff.

Since the discovery by Walker that patients with myasthenia gravis are helped by neostigmine, ideas concerning the nature of myasthenia gravis have been focused about three theories: (1) excessive destruction of acetylcholine due to unusually large amounts of choline esterase (demonstrated as unlikely by Milhorat), (2) defects in the ability of muscle to utilize acetylcholine (disproved by Lanari and Harvey and collaborators) and (3) decrease in the synthesis or release of acetylcholine.

The most plausible hypothesis is that there exists a defect in the synthesis of acetylcholine in patients with myasthenia gravis. Dr. Otto Loewi suggested that such synthesis be investigated. We are immeasurably indebted to Dr. Loewi for his enthusiastic interest in the development of the problem.

The synthesis of acetylcholine was studied according to a modified method of Quastel, Tennenbaum and Wheatley (*Biochem J.* 30:1668, 1936). Uniform samples of nerve tissue, frog brain, for instance, under standard environmental conditions will synthesize acetylcholine at a fixed rate. The amount of acetylcholine synthesized was biologically assayed by measuring its effect in inducing contraction of the physostigminized rectus abdominis muscle of the frog. The relative ability of

he pyramidal tract; besides, there were bilateral cerebellar signs, presumably due to implication of the olivo-cerebellar tracts as they crossed. This was remarkable: Here was a lesion so situated that it seemed as if the interruption of pathways could have been made by a knife's cutting straight down, without any spread to the side; there was, for example, no evidence of involvement of structures even as slightly lateral as the hypoglossal nerves; one might have suspected some sign of impairment of this nerve, but the most careful search did not show it.

Another point worth mentioning is the "onion peel" type of trigeminal impairment. This condition is rarely seen, and, so far as I know, it has never been explained.

DR. H. A. RILEY: Cases of congenital changes in his vicinity are interesting. My colleagues and I had a patient at the institute with this condition, the so-called platybasia, or basilar invagination, with, as I remember the case, almost complete unilateral involvement of all the cranial nerves on the left side from the sixth down. This patient did not have any particular cerebellar signs; neither did he have any sensory lesions or signs referable to the pyramidal tract. He showed the same typical disturbance in the relation of the skull to the vertebral column as did Dr. Meyer's patient, only to a greater degree, and we accepted the diagnosis of platybasia. We were not able to explain satisfactorily why all the signs were unilateral, and after considerable study of the patient, with observation of increased protein in the spinal fluid, we were unwilling to rest on the diagnosis, because we thought the patient might have a flat area of meningioma on one side. The patient was operated on, but no meningioma was encountered. The patient is in the Goldwater Memorial Hospital with the same disturbance, namely, involvement of the cranial nerves on the left side from the sixth down, without any involvement of the cranial nerves on the right side or disturbance referable to the pyramidal tract. I think it is accepted that these disturbances of the cranial nerves are produced by tension and gradual degeneration of the cranial nerve particularly pulled on by the angulation of the stem.

In this presentation one feature should be mentioned articularly, the caudal migration of the medulla. The medulla actually does not migrate caudally in this condition or in the Arnold-Chiari deformity. What seems to happen is a premature fixation of the spinal cord caudally so that all the segments of the spinal cord and the medulla come to lie opposite portions of the segmented axis which are usually in relation to more caudal segments of the neuraxis. Under ordinary circumstances the spinal cord is drawn up within the vertebral canal until the conus lies opposite the disk between the first and the second lumbar vertebra. Under abnormal conditions the medulla and all the spinal segments are in relation to normally more caudally situated axial segments. The real situation is the interference with the normal ascent of the neuraxis within the vertebral column, so that it is not a caudal migration but a caudal displacement due to failure of ascent. In this case the enlargement of the foramen magnum was a definite indication that this condition was present. I did not see anteroposterior roentgenograms of the spinal axis, and I do not know whether any were taken. If such exposures had been made, it would probably have been seen that the upper part of the cervical canal was much larger than it should have been normally, in correspondence with the enlarged foramen magnum.

DR. BYRON STOOKEY: It is extremely difficult to accept Dr. Brickner's suggestion of a discrete lesion in the midline in this case. The scheme shows a split in the midline lying dorsal to the axis, and the roentgenograms show that the constructive process has extended into the foramen magnum. There are present therefore compression from the dorsal aspect by a cyst and compression from the ventral aspect; I do not see therefore how one can say this is a discrete lesion in the midline. It is entirely probable that the cyst compressed the dorsal columns and their nuclei and the rather large odontoid process extending forward compressed the ventral aspect of the axis, so that with compression of the spinal cord by two such space-occupying lesions within the foramen magnum it is. questionable whether one should accept the diagnosis of a lesion "which can be drawn like a knife down the midline" and implicates the decussations of the trigeminal area. It seems to me that a definite mass occupies this entire area.

When I saw the roentgenogram, I thought the foramen magnum was enlarged. I should like to know whether Dr. Cohen and Dr. Meyer thought the foramen magnum was larger than normal, and whether it appeared to be so at operation.

DR. IRA COHEN: In answer to Dr. Stookey's question, the foramen magnum was enlarged rather than deformed, as it is supposed to·be in basilar platybasia. In another case of basilar platybasia, I recall that the foramen was deformed, being triangular rather than enlarged.

DR. RICHARD BRICKNER: Dr. Stookey probably misunderstood me; if I used the word "lesion" I did not mean to do so. I was simply describing the clinical and anatomic picture the patient showed, regardless of the pathologic nature of the lesion.

DR. B. C. MEYER: In reply to Dr. Riley's question, I must explain that the artist who made the drawing erroneously introduced a few extra spinal nerves.

The roentgenologist did not interpret the foramen magnum as being pathologically enlarged.

I should like to add to what Dr. Stookey has said about Dr. Brickner's emphasis on involvement of some of the decussations in the medulla. First, I do not believe that one need postulate the presence of a lesion of the decussations in order to explain the "onion peel" type of hypalgesia of the peripheral aspects of the face. The latter can be accounted for by the involvement of the descending roots of the fifth nerve bilaterally. Second, in so far as the tumor was in the midline it affected structures in the midline. The fact, then, that the decussations were involved must be regarded as fortuitous, as was indicated by the prompt recovery of their functions after operation.

Meningocele Treated by Destruction of the Choroid Plexuses: Report of Cases. DR. TRACY J. PUTNAM.

In many cases of meningocele repair of the defect leads to development of hydrocephalus, and some of the most satisfactory cures from destruction of the choroid plexuses have been in such cases. In other cases plastic repair of the meningocele is rendered difficult or impossible because of the tension within the sac.

Three cases of meningocele are reported in which endoscopic cauterization of the choroid plexus was carried out as a primary operation. All the patients had been seen at other clinics; in 2 cases operation was considered impossible, and in the third it was attempted and abandoned. The third case was an unusual instance of interfrontal meningocele, which has shrunk to a nubbin of tissue after reduction of the intracranial pressure. In the other 2 cases the sac was in the lumbar region. In 1 of these cases the sac, which had been leaking

experiments errors resulting from the difference of concentration of the enzyme in the different parts of the brain are probably eliminated. This procedure may also account for the relatively uniform results we obtained.

That results using serum of patients with myasthenia gravis differ from ours may be only an apparent contradiction. The fact that one is unable to demonstrate any difference in the amounts of acetylcholine synthesized in the presence of serum of control subjects as compared with that synthesized in Locke's solution indicates that the method is not sensitive enough to demonstrate slight differences in synthesis due to the presence or absence of substances in the serum

of patients with myasthenia gravis. Possibly the use of rat brain introduces such a large amount of substrate as compared with the concentration of the enzyme that the requirements of the enzyme are completely fulfilled, so that the addition of more substrate in the form of serum is immaterial.

The statement that the addition of relatively large amounts of minced thymoma to the mixture did not modify the synthesis of acetylcholine may be due to the fact that presentations of thymoma contain large amounts of substances which potentiate the synthesis of acetylcholine, such as carbohydrates and amino acids, so that the effect of an inhibitor substance, if present, could be masked.

Book Reviews

Manual of Military Neuropsychiatry. Edited by Harry C. Solomon, M.D., Professor of Psychiatry, Harvard Medical School, and Paul I. Yakovlev, M.D., Clinical Director, Walter E. Fernald State School, Waltham, Mass., with the collaboration of other authorities. Price, $6. Pp. 764, with illustrations. Philadelphia: W. B. Saunders Company, 1944.

This is an excellent and timely addition to any neuropsychiatric library, even though it has been written primarily as a source of reference for the use of medical officers in the military services. It contains a great deal of practical material and up-to-date knowledge in connection with current neuropsychiatric problems in the armed forces, written by many of the most eminent authorities in the field of neuropsychiatry. Of the forty-six contributors, twenty are in active military service.

This manual represents an expansion of a series of lectures of the "Seventh Post-Graduate Seminar in Neurology and Psychiatry, Including a Review Course in Military Neuropsychiatry," held at the Metropolitan State Hospital, Waltham, Mass., in 1941-1942. These lectures were privately published by the late Colonel Roy D. Halloran, superintendent of the hospital and director of the seminars. Because of the great demand for copies of the lectures from medical officers in the military services, Canada and overseas, and the limited supply, there resulted the present manual, which was planned to make them available to a large public. The manual is intended as a reference text on topics of clinical neurology and psychiatry and has been prepared especially for medical officers who, under the conditions of service in areas often remote from libraries, textbooks and other sources of readily accessible neuropsychiatric information, are deprived of these facilities. It should be noted, however, that the manual will be found useful by nonmilitary psychiatrists and others who are directly or indirectly interested in the psychiatric field.

The book is divided into an introductory chapter, written by Lieut. Col. Douglas A. Thom and Col. Roy D. Halloran, and five sections, entitled "Induction," "Administration and Disposition," "Clinical Entities," "Prophylaxis and Therapy" and "Special Topics." It is stressed that it has been difficult to assemble all the material on the prophylaxis and therapy of neuropsychiatric casualties, as a great deal of information pertaining to these specifically military aspects of neuropsychiatry is still restricted matter, and will remain so, probably until the termination of the war.

The manual contains a series of forty-nine articles. Section II considers such topics as neuropsychiatric screening at induction stations, military medical administration of induction stations, methods for rapidly securing a recorded personal history of inductees and psychiatric and neurologic examination of inductees. Section III discusses organization of the medical department and the duties of medical officer neuropsychiatrists; military laws and regulations pertaining to disposition of neuropsychiatric casualties; disposition of neuropsychiatric cases in the Army, the Air Forces, the Navy and the Merchant Marine at station hospitals and military camps, and military forensic neuropsychiatry.

Section IV, on the "Clinical Entities," has articles on "Psychoneurosis and Psychomatic Disorder," by Jacob B. Friesinger and Stanley Cobb; "Psychopathic Personalities," by William Malamud; "Alcohol and Alcoholism," by Edward A. Strecker; "Sexual Deviates," by Abraham Myerson; "Malingering," by Abraham Myerson; "Feebleminded and Defective Delinquents of Draft Age," by Ransom A. Greene and C. Stanley Raymond; "Epilepsy and Paroxysmal Neuropsychiatric Syndromes," by William G. Lennox; "Acute Psychotic Episodes and Acute Confusional Turmoil States in Soldiers," by Col. W. C. Porter; "Principal Psychoses," by Gaylord P. Coon, and "Common Diseases of the Nervous System and Syphilis of the Nervous System," by H. Houston Merritt. In other neurologic articles such topics are discussed as meningitis and encephalitis in the military services; peripheral nerve injuries and spinal cord injuries; craniocerebral injuries, and posttraumatic syndromes.

Section V includes chapters on "Psychology and Morale," "Mental Hygiene Clinics in Military Installations" and "Management of Neuropsychiatric Casualties in the Zone of Combat," by Lieut. Col. Roy B. Grinker and Major John P. Spiegel; "Emergency Care and Treatment of the Acute War Neurosis," by Lawrence S. Kubie; "Military Group Psychotherapy," "Rehabilitation of Military Offenders and Treatment of Alcoholic States," by Lieut. Col. Wilfred Bloomberg; "Shock Therapy in the Military Services," by Harry C. Solomon, and "Custodial Care and Management of Psychotic Soldiers and Occupational Therapy," by F. H. Sleeper.

In the section on special topics, or section VI, there are chapters on neuropsychiatric aspects and treatment of convoy and torpedo casualties, physiology of flying

two mediums to influence the synthesis of acetylcholine can thus be measured. In the study to be reported the effect on the synthesis of acetylcholine of serums from patients with myasthenia gravis was compared with the effect on the synthesis of acetylcholine of control serums.

Five healthy subjects and 57 patients with diseases other than myasthenia gravis served as controls. The amount of acetylcholine synthesized in the presence of the control serums during incubation for four hours at 37 C. averaged 2.08 micrograms per hundred milligrams of frog brain. The amount of acetylcholine synthesized in the presence of serum of control subjects deviated from the average not more than ± 15 per cent.

The amount of acetylcholine synthesized in the presence of serum of patients with myasthenia gravis was in all cases less than that synthesized by the control serum. The greatest defect was observed in the most seriously ill patient. The amount of acetylcholine synthesized in the presence of serum of patients seriously incapacitated with myasthenia gravis was less than half that synthesized by the control serum.

Spinal fluid exerted an effect similar to that of serum on the synthesis of acetylcholine. The effect of the spinal fluid of patients with myasthenia gravis on the synthesis of acetylcholine was compared with the effect of spinal fluid of patients with diseases other than myasthenia gravis. Here, also, a defect in the synthesis of acetylcholine was observed in patients with myasthenia gravis. The percentage of the defect in the presence of the spinal fluid of patients with myasthenia gravis was similar to the percentage of the defect in the presence of serum of the same patient.

Conclusion.—The decrease in synthesis of acetylcholine is apparently specific for myasthenia gravis, since it does not occur with other diseases presenting debility, cachexia, immobility and prostration. Also, the magnitude of the defect in the synthesis of acetylcholine is related to the severity of the myasthenia gravis. This depression of synthesis of acetylcholine in vitro suggests that there is a similar defect in the synthesis of acetylcholine in the body of patients with myasthenia gravis. It is probable that in patients with myasthenia gravis the acetylcholine available at the synapses eventually becomes insufficient for effective and repeated contraction of the muscle. This may manifest itself clinically in fatigability and muscular weakness. Neostigmine aids these patients by impeding the breakdown of the diminished quantities of acetylcholine.

Since the decreased synthesis of acetylcholine may be due to several factors, namely (1) lack of precursor substances, (2) lack of potentiator substances and (3) excess of inhibitor substances, several substances normally occurring in the body are being studied as to their effect on synthesis of acetylcholine in vitro.

DISCUSSION

Dr. HERBERT C. STOERK: Because of the possible correlation between thymic tumor and myasthenia gravis, Mrs. Elvira Morpeth and I have studied the synthesis of acetylcholine in the rat brain according to the method of Quastel and associates in the presence of tissue from a thymoma which was obtained from a patient who died of myasthenia gravis and on whom autopsy was performed at the department of pathology of the College of Physicians and Surgeons. We then repeated the experiments of Torda and Wolff and studied the synthesis of acetylcholine, according to the method of Quastel and associates, in the presence of serum of patients with myasthenia gravis. We used rat brains instead of frog brains. We examined the

serum of 6 patients whose condition had been diagnosed as myasthenia gravis at the Neurological Institute of New York, 2 of whom had severe symptoms. None of the samples examined showed any difference in the amount of acetylcholine formed after incubation, whether thymic tissue or serum from a patient with myasthenia gravis was added. I should like to ask Dr. Wolff and Dr. Torda whether they ever used brain tissue other than that of frogs.

Dr. HAROLD G. WOLFF: That there is something wrong with the synthesis of acetylcholine in patients with myasthenia gravis must have occurred to investigators many times. I am sure that it has been put to test, I assume with negative results; otherwise, the defects in synthesis of this substance in patients with myasthenia gravis would have been called to the attention before this. The method which Dr. Torda has evolved has come through several phases, starting originally, as she mentioned, with the method of Quastel, Tennenbaum and Wheatley; she has modified this technic so that at present it looks as though one could demonstrate by means of her procedure a difference in the synthesis of acetylcholine in patients with myasthenia gravis. I call attention to the fact that this method is not as simple as it looks. If one takes the synthesis of control serum as 100 per cent, the serum of the patient so sick that she is barely able to breathe supports a synthesis of 40 per cent. That, after all, is not a great difference. Indeed, patients who have obvious but local myasthenia, with failure in ability to raise one eyelid, may have no demonstrable defect in synthesis. It is apparent, therefore, that we are working with a gross instrument, and that we are pointing out gross defects. I am sure that any subtlety in defect in synthesis is not shown. Although it may be assumed for the moment that the differences observed are valid (and these inferences will be challenged, and rightly so), difficulties still present themselves. Why is it that a defect so widespread as this seems to be if it can be demonstrated in the serum, would affect but a limited portion of the body? Why should the weakness be peculiar to the muscles about the eyes, perhaps for several years? If there is something in the blood stream which affects synthesis, why are not all muscles involved as are the ocular muscles? One is obliged to postulate that there is a difference in sensitivity in different nerve tissues. Dr. Torda has made assays for a few substances commonly found in the body to find out whether they are capable of modifying synthesis in the manner described. Extracts of the thyroid gland, salivary gland and lymph gland have no depressor effect. Extracts of thymus in very small amount interfere with synthesis. Pancreatic extracts also interfere with synthesis. Minced thymus in larger amounts accelerates the synthesis. Whether these observations have any bearing on the role of the thymus and pancreas in myasthenia gravis I am not prepared to say.

I should say, in closing, that we have a concept of the nature of myasthenia gravis. Persons with this disease are not capable of adequately supporting the synthesis of acetylcholine, an important substance in contraction of skeletal muscle.

Dr. CLARA TORDA: We did not use rat brain for two reasons: (1) Under the circumstances of analysis, the percentage concentration of the enzyme which synthesizes acetylcholine is lower in the rat brain than in the frog brain, and (2) we used 100 mg. samples of a homogenized mixture of minced fresh brain of 28 frogs (100 mg. of tissue taken from one rat brain contains only a part of the brain). Therefore in our

ever, will miss observations on the effect of emotional factors in the genesis of this disorder. A critical evaluation by clinicians of the role of such factors would be of interest in the psychiatric field. An important observation which adds to the fund of facts in psychosomatic medicine is their observation on the effect of emotion on renal blood flow. During the investigative procedure on renal blood flow, 3 patients were frightened and experienced a serious state of alarm. The objective signs were pronounced sweating, pallor, restlessness and apprehension. During this period the renal blood flow decreased notably, and the filtration fraction increased, a condition indicating psychogenic vasoconstriction of the efferent glomerular arterioles.

The authors are frank to state that at present the etiologic factors in hypertension are unknown. They suspect a humoral mechanism with superimposed neurogenic factors.

This book is highly recommended.

One Hundred Years of American Psychiatry. Published by the Columbia University Press. New York: Columbia University Press, 1944. Price, $6. Pp. 650.

This volume was conceived several years ago, with the purpose of presenting a history of American psychiatry as a memorial for the centennial celebration of the American Psychiatric Association. The volume is intended to be a historical review of the evolutionary synthesis of a century of American psychiatry, and it stresses psychiatry as a growing cultural force. A chapter, entitled "Presenting this Volume," by Dr. Gregory Zilboorg, and a general historical survey, by Dr. G. K. Hall, serve as an introduction.

The book is composed of fourteen chapters, three of which deal with military psychiatry. Much time has been spent in research in the production of this book, and it is an excellent volume for historical reference. Included in the book are photographs of the original founders of the American Psychiatric Association and facsimiles of the signatures of the various presidents and the thirteen founding members. One of the defects of the work is the repetition of factual historical data. This is in part unavoidable, since each chapter is written by a different person.

Dr. Richard H. Shryock is the author of the chapter entitled "The Beginnings: From Colonial Days to the Foundation of the American Psychiatric Association." Dr. Henry E. Sigerist describes "Psychiatry in Europe at the Middle of the Nineteenth Century." An excellent chapter by Dr. Winfred Overholser covers the history of the founding and the founders of the association. Dr. Samuel Hamilton describes the history of the American

hospitals for mental disease, and Dr. John C. Whitehorn reviews a century of psychiatric research in America. Dr. William Malamud contributes a survey of the history of psychiatric therapeutics, and Dr. Albert Deutsch reviews the history of mental hygiene. Military psychiatry is reviewed in terms of the advances made during the periods of the American Civil War, World War I and the present global war. In additional chapters the relation of psychology to psychiatry, the legal aspects of psychiatry and the influence of psychiatric thought on anthropology are reviewed.

A New German-English Psycho-Analytical Vocabulary. By Alix Strachey. Published by the Institute of Psycho-Analysis. Price, $2.50. Pp. 85. Baltimore: Williams and Wilkins Company, 1943.

This small volume, published by the Institute of Psycho-Analysis as one of the research supplements to the *International Journal of Psycho-Analysis*, is a timely and useful book. It aims to bring English translations of psychoanalytic literature up to date with modern German terminology and records the expansion and standardization of the vocabulary of psychoanalysis.

It is primarily designed to assist translators of psychoanalytic literature. The volume is an enlargement of what was formerly "The Glossary for the Use of Translators of Psychoanalytic Works."

It is recommended as a useful addition to the literature of every psychiatrist who is interested in reading psychoanalytic literature in the original German text.

News and Comment

THE SCIENTIFIC EXHIBIT, NINETY-FIFTH ANNUAL SESSION OF THE AMERICAN MEDICAL ASSOCIATION

Application blanks for space in the Scientific Exhibit at the Ninety-Fifth Annual Session of the American Medical Association, to be held at Philadelphia, June 18 to 22, 1945, are now available. Applications must be made on or before Feb. 12, 1945. The representative to the Scientific Exhibit from the Section on Nervous and Mental Diseases is Dr. F. P. Moersch, Mayo Clinic, Rochester, Minn.

Requests for application blanks may be addressed to Dr. Moersch or to the Director, the Scientific Exhibit, American Medical Association, 535 North Dearborn Street, Chicago 10.

and neuropsychiatric experiences of the foreign armies, as well as an article on electroencephalography, by Frederic A. Gibbs, which is especially well written and illustrated, with the addition of the latest bibliographic references on the subject. Most of the articles are sufficiently detailed to be considered good reference material, particularly since the latest bibliographic material is included.

The index, which contains sixty-seven double column pages, is especially valuable because of its fine detail, enabling one to obtain rapid and easy reference to the desired information.

Young Offenders: An Enquiry into Juvenile Delinquency. By A. M. Carr-Saunders, Hermann Mannheim and E. C. Rhodes. Pp. 168. New York: The MacMillan Company, 1944.

"Young Offenders," a volume of 168 pages, was written by A. M. Carr-Saunders, director of the London School of Economics, and Dr. E. C. Rhodes, reader in statistics and Dr. Hermann Mannheim, lecturer in criminology, both on the staff of the same school.

The authors worked under the auspices of the home office of the British government, which undertook an investigation of juvenile delinquency. The investigation began in October 1938 and covered the London area and six provincial cities.

The first of the book's four chapters deals with the history of previous investigations and cites many reports in part. The earlier reports were in general unsystematic and lacking in comparable standards, and the conclusions drawn were open to question. There was, however, a certain amount of uniformity of opinion, viz., concerning the predominant factors in juvenile delinquency.

These factors are: (a) the family factor—the broken home; (b) the environmental factor, in particular, educational mistakes or lack of education; unfavorable economic conditions, in particular, unsuitable or complete lack of employment, and the dangers inseparable from the growth of towns; (c) physical and mental defects, and (d) unsuitable methods of dealing with young offenders.

The earlier investigations, dating as far back as the post-Napoleonic period, were concerned primarily with the harm done by over-harsh penal methods and lack of education, and did not begin to take account of the psychologic factors. The present investigators, however, had hoped to make a parallel inquiry into the psychologic aspects; but, unfortunately, the war intervened, and their plans were not realized.

In the second chapter an attempt is made to disclose trends in juvenile delinquency, from a demonstration of statistical data collected during the present century. This examination was made with particular regard to (a) increasing juvenile crime; (b) geographic distribution; (c) age distribution, and (d) ratio of the frequency of adult crime to that of juvenile crime. Here, again, the authors encounter the difficulties inherent in analysis of statistical compilations not having comparable standards, with the added difficulty of frequent changes in legal position during the period covered.

The present investigation, covered in chapter 3, is restricted to recording of data relative to social and environmental conditions. The medical side was omitted. The investigation took six months, and the procedure consisted in recording information received from the probation office and the London City Council. Information was also recorded for nondelinquent youth (as a control) by the use of school data, an attempt being

made to use a mate of the same age for each delinquent subject. Actually, the cases of 1,953 delinquent and 1,970 control children were investigated.

Special cards were designed for the recording of the data. These were obtained from replies to questions about the home, parents, siblings, cousins, aunts, uncles, etc., and environmental conditions and influences. These answers were recorded according to certain standards, for example, good, fair or bad. In the final chapter the authors summarize their conclusions and comment that the reader may be disappointed since their report does not adequately answer the question why juvenile delinquency has increased.

No single influence, characteristic or tendency could be described that would account for juvenile delinquency. Statistics are not enough. The problem cries out for psychologic understanding, and the authors are fully aware of this fact. Again and again the authors are compelled to express the hope that the psychiatrist can explain the inconsistencies which statistics reveal. They state: "There are boys, neither living under abnormal influences nor showing subnormal characteristics, so far as our data go, who become delinquent . . . and on the other hand, boys subject to abnormal influences and showing subnormal characteristics who do not become delinquent."

The book is difficult reading. Unless one has statistical yearnings, one is wafted away. On the other hand, if one can persevere, there is much to be gleaned. What the book fails to reveal challenges the psychiatrist.

Hypertension and Hypertensive Disease. By William Goldring and Herbert Chasis. Price, $3.50. Pp. 253, with 53 illustrations. New York: Commonwealth Fund, 1944.

The authors have written about a subject of which they have extensive clinical experience. They are to be commended for their knowledge and their application of physiologic processes and technics in the elucidation of the problem of hypertension. The book is not meant as an encyclopedic treatise on hypertension but represents a body of opinion based on facts obtained by the authors in their own experience. The point is stressed that hypertensive disease and the therapeutic methods used for overcoming it cannot be evaluated in terms of the level of the blood pressure alone. The use of this criterion is shown to be a common error. It is the authors' opinion that hypertension continues unchanged despite any effect on the level of the blood pressure, and that the latter is merely a secondary sign of, and not a causative factor in, hypertensive disease.

Their most fruitful section is the portion that deals with the specific hemodynamic changes and the renal functional and renal hemodynamic alterations associated with hypertension. Determinations of these factors are based on special physiologic methods in clinical medicine which the authors have used to good advantage. Their data indicate that in the great majority of patients hypertension does not result from a mechanism similar to that shown by Goldblatt in experiments with dogs. Few cases of hypertension caused by this mechanism have been encountered in their experience. They demonstrate that renal blood flow is normal in the early phases of hypertension and that it becomes impaired only much later in the course of the disease. Therefore, the renal disturbance is not primary but secondary.

There is a discussion of medical and surgical treatment. The authors indicate that psychotherapeutic management is one of the most important phases of the treatment of hypertension. Neuropsychiatrists, how-

INDEX TO VOLUME 52

The asterisk (*) preceding the page number indicates an original article in the Archives. Subject entries are made for all articles. Author entries are made for original articles and society transactions. Book Reviews, Obituaries and Society Transactions are indexed under these headings in their alphabetical order under the letters B, O and S, respectively.

Abdomen: See also Gastrointestinal Tract; etc.
  abdominal muscle reflex, *353
  abdominal skin reflex, *351
  paroxysmal pain; form of focal symptomatic epilepsy, 158
Abnormalties and Deformities: See Twins; and under names of organs and regions, as Atlas and Axis; Cerebellum; etc.
Abscess: See under names of organs and regions, as Brain, abscess; etc.
Acetylcholine: See Choline and Choline Derivatives
Acid, hippuric, synthesis in dementia precox, *57
  Nicotinic: See Nicotinic Acid
Ac-tetrahydro-b-naphthylamine, abolition of bulbocapnine catalepsy in cat by, *61
Activity, effect of controlled temperatures on spontaneous activity rhythms of albino rat, 236
  synchronization of spontaneous activity in denervated human muscle, *495
Adenoma, mixed, of hypophysis, 420
  physiologic and psychologic studies in spontaneous hypoglycemia, 331
  surgical removal of adrenal adenoma with relief of Cushing syndrome, 421
Adipose Tissue: See Lipoma
Adrenalectomy: See under Adrenals
Adrenals, hemorrhage; fulminating meningococcic infection with bilateral massive adrenal hemorrhage (Waterhouse-Friderichsen syndrome), 420
  surgical removal of adrenal adenoma with relief of Cushing syndrome, 421
Age, distribution of acetylcholine in brains of rats of different ages, 147
  electroencephalographic evaluation of psychopathic personality; correlation with age, sex, family history and antecedent illness or injury, *515
  incidence and prognosis of epilepsy, 76
  influence on effect of thyroidectomy in rhesus monkey, 422
  Old: See Old Age
Agranulocytosis following malarial therapy in general paresis, 240.
Air, Compressed: See Caisson Disease
  Pressure: See also Altitude
  pressure; effects of low atmospheric pressures on activity of thyroid, reproductive system and anterior lobe of pituitary in rat, 240
Air Raids, effect of war on civilian population in England, 245
Alcohol, Addiction: See Alcoholism
  clinical steps in metabolism of alcohol by brain in vitro, 72
Alcoholism: See also Korsakoff Syndrome: Liver, cirrhosis
  central necrosis of corpus callosum (Marchiafava-Bignami's disease); report of case in American man, with comments on pathogenesis of disease, 151
  electroencephalogram associated with chronic alcoholism, alcoholic psychosis and alcoholic convulsions, *290
  personality study of alcohol addiction, 331
Allergy: See Anaphylaxis and Allergy
Alpers, B. J.: Clinical and pathologic features of gliomas of spinal cord, *87
Altitude: See also Air, pressure
  high; cerebrospinal fluid pressure under conditions existing at high altitudes; critical review, *400
  intracranial pressure in human subject at, *520
  nature and origin of altitude pains, 416 .
Amentia: See Mental Diseases; etc.
Amnesia, retrograde, 332

Amphetamine: See Mental Diseases
Amputation, effects of denervation and amputation of hindlimbs in anuran tadpoles, 144
Amyotrophy: See Sclerosis, amyotrophic lateral
Anaphylaxis and Allergy: See also Asthma; etc.
  pathology of demyelinating diseases as allergic reaction of brain, *443
  some aspects of mind in asthma and allergy, 73
Androgens: See also Hormones, sex
  constancy of concentration in urine, 422
  influence of estrogen and androgen on chemical constituents of brain, 337
  stimulation of mammary glands in hypophysectomized rats by estrogen and testosterone, 421
Anesthesia, neurologic complications following use of continuous caudal anesthesia, *531
  pentothal sodium anesthesia in neurologic surgery, 544
  so-called "aseptic or chemical meningitis" (following spinal anesthesia), 150
Anesthetics: See Anesthesia
Aneurysm, cerebral; report of unusual case, 160
  congenital, of cerebral arteries, 150
Angina, Agranulocytic: See Agranulocytosis
Angiospasm: See Brain, blood supply
Anomalies: See under names of organs and regions
Anoxia: See Oxygen, deficiency
Anxiety: See also Neuroses and Psychoneuroses
  guide to interviewing and clinical personality study, *197
  states in Navy, 74
Apparatus: See also Instruments
  motor nerve function with lesions of peripheral nerves; quantitative study, *317
Arachnoid; arachnoidal fibroblastoma (meningioma) with metastases to liver, 417
Argyll Robertson Pupils: See under Pupils
Arieff, A. J.: Cerebellar ataxia associated with cerebral signs, 79
Armed Forces Personnel: See Military Medicine; Naval Medicine; Soldiers and Veterans; etc.
Arms: See also Extremities; Humerus; etc.
  biceps reflex, *345
  paradoxic triceps reflex, *345
  triceps reflex, *345
Arsenic and Arsenic Compounds: See also Arsphenamines
  arsenical encephalopathy, 334
  hemorrhagic encephalopathy following arsenical therapy, 151
Arsphenamines, genesis of encephalopathy due to, 417
Arteries: See also Aneurysm; Blood pressure; Thrombosis; Vasomotor System; etc.
  carotid; cerebral aneurysm; report of unusual case, 160
  cerebral: See Brain, blood supply
  relation of circulus arteriosus to hypothalamus and internal capsule, *526
Arthritis, rhizomelic spondylosis (rheumatoid arthritis of spine), with compression of cord; report of case, 162
Artificial Fever Therapy: See Dementia Paralytica; Neurosyphilis
Asthenia, neurocirculatory; effort intolerance in soldiers, 239
Asthma: See also Anaphylaxis and Allergy
  psychologic factors in, 149
  some aspects of mind in asthma and allergy, 73
Astrocytoma of spinal cord, *391
Ataxia, cerebellar, associated with cerebral signs, 79
Atlas and Axis, abnormalities; basilar impression resembling cerebellar tumor; report of case, *412
  abnormalities; platybasia; report of case, 552
Atrophy, Muscular: See Dystrophy, muscular
Axons: See Neurons

Babinski Sign: See Reflex
Bacteria: See also Meningococci; etc.
  coli, infected subdural hematoma in infants associated with meningitis due to, 423

ARCHIVES OF

NEUROLOGY AND PSYCHIATRY

VOLUME 52
1944

CONTENTS OF VOLUME 52

DECEMBER—*Continued*

CONTENTS OF PREVIOUS NUMBER

MARCH 1944. NUMBER 3

APRIL 1944